FDA Briefing Document

Gastrointestinal Drugs Advisory Committee

July 14, 2004

Zelnorm® for Treatment of Chronic Constipation

Gastrointestinal Drugs Advisory Committee on Zelnorm® for Treatment of Chronic Constipation

FDA Briefing Document

Novartis Pharmaceuticals Corporation submitted a Supplemental New Drug Application (21-200/S-005) on October 20, 2003 seeking approval of Zelnorm (6 mg bid) for the treatment of chronic constipation. Zelnorm is a 5-HT_4 partial agonist with moderate affinity for the 5-HT_1 receptor. It was first approved in July 2002 for the short-term treatment (4-6 weeks) of women with constipation predominant irritable bowel syndrome (c-IBS). The therapeutic mechanism of action is based primarily on its agonist action on 5-HT_4 receptors, resulting in augmented bowel motility, increased intestinal secretion and inhibition of visceral sensitivity. Two clinical studies were submitted in support of the chronic constipation indication.

This briefing document for the Gastrointestinal Drugs Advisory Committee meeting consists of three sections:

1. Clinical Summary of Efficacy (pages 4-16)
2. Clinical Summary of Safety (pages 17-64)
3. Draft Statistical Review and Evaluation (pages 65-118)

This document contains information from IMS Health National Prescription Audit Plus and is not to be used outside of the FDA without prior clearance by IMS Health.

Issues for Discussion:

1. Efficacy
    a. Discuss the appropriateness of a primary efficacy endpoint of an increase of =1 complete spontaneous bowel movement per week vs. =3 complete spontaneous bowel movements per week.
    b. Only 9 to 16% of subjects were =65 years of age and the treatment effect was significantly smaller in older patients. Are these data adequate for an indication that is common in the elderly?
    c. Only 9 to 14% of the subjects were male and the treatment effect was smaller in males than females. Are these data adequate to support approval of Zelnorm for use in the treatment of chronic constipation in males?
    d. Is the population studied representative of patients with chronic idiopathic constipation?

e. Are the clinical trial data adequate with respect to the population with chronic constipation that is likely to be treated with Zelnorm?
f. Is Zelnorm effective for the treatment of chronic constipation?

2. Safety
    a. Post-marketing cases of ischemic colitis and serious complications of diarrhea were not limited to patients with IBS. What are the implications of these adverse events for patients with chronic constipation?
    b. The incidence of diarrhea and discontinuations due to diarrhea was higher in patients =65 years of age. Is there sufficient information that Zelnorm is safe for use in this age group?
    c. Do the adverse event data from the clinical trials and post-marketing surveillance provide adequate evidence of safety of Zelnorm for the treatment of chronic constipation?
    d. Should the information on the post-marketing cases of ischemic colitis and intestinal ischemia be moved from the PRECAUTIONS section to the WARNINGS section of the package insert?

Clinical Summary of Efficacy

Robert Prizont, M.D., Division of Gastrointestinal and Coagulation Drug Products

I. Background.

Zelnorm® (tegaserod maleate tablets), is a drug with affinity for 5-HT_4 receptors located in the smooth muscle, particularly bowel smooth muscle. The agonist action of Zelnorm on these 5-HT_4 receptors results in augmented bowel motility. On July 2002, Zelnorm was approved for the short-term (4-6 weeks) treatment of women with irritable bowel syndrome (IBS), in whom the primary bowel symptom was constipation (IBS-C). The approved dosage was a 6 mg tablet taken twice a day. To support safety and efficacy of Zelnorm in IBS-C patients, Novartis conducted three randomized, double-blind, placebo-controlled, multi-center studies. Eligible patients were required to have no less than a 3-month history of abdominal pain, bloating and constipation, the classical symptoms of IBS-C according to the Rome Criteria[1]. Approval of Zelnorm® for IBS-C was based on a higher proportion of responders in the Zelnorm® groups compared to the placebo groups. In patients treated with Zelnorm® there was an increase (5%) in diarrhea associated with use of the drug. There was also a small numerical increase in the rate of abdominal surgeries, particularly cholecystectomies. Post-marketing, there have been reports of ischemic colitis, death, hypotension, syncope, and serious complications of diarrhea. The Zelnorm® label has been updated to include these serious adverse events.

In this submission, Novartis proposes the use of Zelnorm® (tegaserod maleate) for the treatment of chronic constipation at a dose of 12 mg/day (6 mg bid). Chronic constipation is a common, benign, functional disorder of the lower gastrointestinal tract, affecting primarily populations in Western countries[2]. The presently accepted definition of constipation includes number of bowel movements as the main objective evidence to assess constipation, plus the subjective symptoms of straining, lumpy stools, and sensation of incomplete evacuation. The Rome II Criteria summarizes the consensus on the definition of functional or idiopathic constipation *(taken from the Lembo and Camilleri article)*.

Table 1. Rome II Criteria for Constipation.
Adults
Two or more of the following for at least 12 weeks (not necessarily consecutive) in the preceding 12 months:
Straining during >25% of bowel movements
Lumpy or hard stools for >25% of bowel movements
Sensation of incomplete evacuation for >25% of bowel movements
Sensation of anorectal blockage for >25% of bowel movements
Manual maneuvers to facilitate >25% of bowel movements (e.g., digital evacuation or support of the pelvic floor)
<3 Bowel movements per week
Loose stools not present, and insufficient criteria for irritable bowel syndrome met[10]
Infants and children
Pebble-like, hard stools for a majority of bowel movements for at least 2 weeks
Firm stools ≤2 times per week for at least 2 weeks
No evidence of structural, endocrine, or metabolic disease

Functional or idiopathic constipation is the most common form of constipation. It affects equally men and women, particularly elderly, and the main complaint is infrequency of BMs. Outlet delay or outlet obstruction constipation, and slow-transit constipation, affect women and represent, in epidemiological studies, a smaller proportion of the constipation population[3,4]. IBS-C is more predominant in younger and middle age women, and manifests by abdominal pain, abdominal distention or bloating as main associated symptoms. There is a plethora of available over-the-counter laxatives, enemas, and bulk-forming agents[5]. Women with outlet constipation are more refractory and less responsive to treatment. Women with IBS-C respond similarly to women with outlet obstruction constipation. Of relevance, improvement of the abdominal symptoms in IBS-C, and outlet obstruction, may parallel improvement in constipation.

II. **Efficacy**.

A. Relevant Points of the Prospective Protocol.

- 2-week baseline, 12-week randomized treatment, 4 week withdrawal period.

- To be randomized, screened patients had to fulfill the constipation criteria, i.e., *(a) less than three spontaneous bowel movements per week that result in a feeling of complete evacuation, (b) at least 25% of stools are very hard and/or hard stools, (c) sensation of incomplete evacuation in at*

least 25% of the bowel movements, and (d) straining on at least 25% of the defecations.

- Three treatment groups: placebo, tegaserod 2 mg bid, tegaserod 6 mg bid.

- Eligible patients had to meet the *Inclusion Criteria*:

  - ✓ Males and females 18 years of age (no upper limit)
  - ✓ History of constipation, as defined above, for at least 6 months before screening. Patients were required to have negative structural bowel disease as demonstrated by a radiology/endoscopy performed during the 5 years prior to the trial.

- Excluded were patients who had the following history or diagnosis:

  - ✓ Evidence of cathartic colon or evidence of laxative abuse,
  - ✓ Chronic constipation due to bowel, gynecological surgery, neurological diseases, connective tissue disorders affecting muscle. Clinical evidence of (including ECG, lab tests) of endocrine/metabolic disorders (including insulin-dependent diabetes), cardiovascular, respiratory, liver, gastrointestinal, hematology, or any disease that may have interfered with patients completing the study.
  - ✓ Organic gastrointestinal diseases affecting the colon *(There was no specific exclusion of IBS patients, by the Rome I or II Criteria)*.

- The *Primary Efficacy Endpoint: the response for the first 4 weeks of double-blind treatment period using the following criterion*:

  - ✓ *A mean increase of I or more complete spontaneous bowel movement (CSBM) compared to baseline*
  - ✓ *At least 7 days in study for the first 4 weeks of double-blind treatment period*

- *Secondary efficacy endpoints* included (1) response rate throughout the 12 weeks of treatment, (2) evaluations of bowel habit (3) QOL.

- Bisacodyl was used as rescue medication. Bulk-forming agents were allowed.

B. Summary of Demographics and Efficacy Results Submitted by Novartis.

To support the use of Zelnorm® (tegaserod) 6 mg bid in chronic constipation, Novartis conducted two multi-center, randomized, double-blind, dose-ranging,

placebo-controlled clinical studies. *The studies, coded by Novartis as Study HTF919E2301 and Study HTF9192302, will be identified here as Studies 2301 and 2302*. *Study 2301* enlisted 128 centers from European countries, Turkey, Australia and South Africa. *Study 2302* enlisted 101 centers from the USA (71), Canada, Argentina, Brazil, Colombia, Venezuela and Chile.

The prospective protocol planned a randomization of 1185 patients in each trial. Study 2301 randomized a total of 1264 patients. Study 2302 randomized a total of 1348 patients. The trials enrolled a *majority* of *women (86-91%),with a mean age of 46-47 years of age, who were Caucasian (84-98%)*.

1. *Study 2301. Relevant Efficacy Results*.

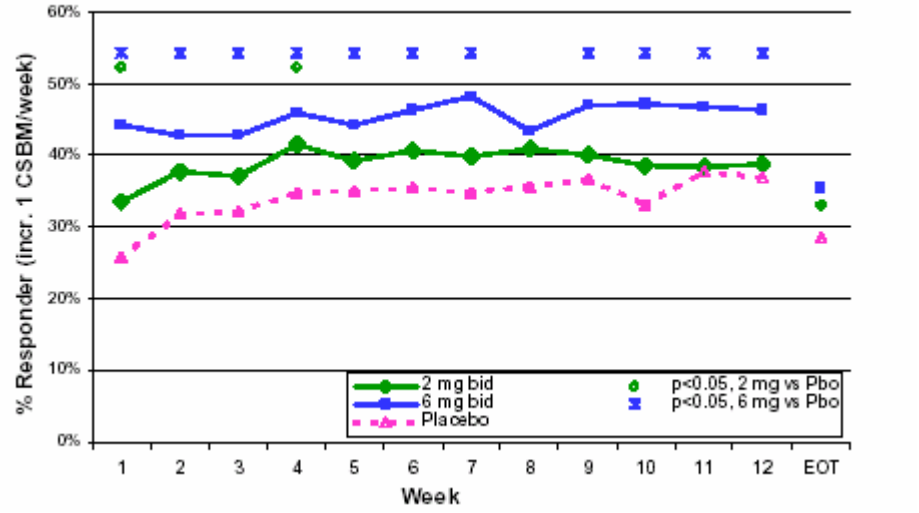
The primary efficacy endpoint was an increase in =1 CSBM/week during the first month of study. The increase in the CSBM/week represents the *average* CSBMs for the 4 weeks, e.g., a patient with 8 CSBMs during the first week of study and no other CSBMs would have *averaged* 2 CSBM/week during the first month. The primary efficacy results are illustrated in the next table. As shown in Novartis Table 9-1, 40% of patients treated with 6 mg tegaserod (*teg 6 mg*), and 36% of patients treated with 2 mg tegaserod (*teg 2 mg*) were responders to the therapy. The placebo (*P*) response of 27% was rather high. These results revealed a *therapeutic gain relative to placebo of 13.5%* for the teg 6 mg, during the first month. The therapeutic gain was lower for the teg 2 mg (*9%*). Differences between tegaserod doses and placebo were statistically significant.

Table 9-1 **Primary efficacy variable: response rate for CSBM during Weeks 1-4 (ITT population)**

	Teg 2 mg bid N = 417	Teg 6 mg bid N = 431	Placebo N = 416
Weeks 1-4			
n	410	428	412
Number of responders (n %)	146 (35.6%)	172 (40.2%)	110 (26.7%)
Odds ratio[1]	1.57	2.04	
95% CI for odds ratio	1.14, 2.16	1.48, 2.80	
p-value[2]	0.0059	<0.0001	

The difference between the teg 6 mg and placebo remained statistically significant over the 12 weeks of study, although *therapeutic gain relative to placebo was only 12.6%*. Assessment of drug responses for the entire length of study, revealed no significant difference between placebo and the 2 mg tegaserod dose. The loss of a significant therapeutic gain in the 2 mg teg was largely due to a 4% increase in placebo response over the 12 weeks of study. The weekly response over the 12 week study period is graphically illustrated in the Novartis Figure 9.1 shown below.

Figure 9-1 Weekly response rate in CSBM (ITT population)



The degree of therapeutic gain is decreased if responders are defined as those patients who no longer meet the definition of constipation (<3 BM/week). As seen in Novartis Table 9-3, in the first month, only *22%* of the 6 mg teg patients were responders who no longer met the definition of constipation. Although the difference against placebo is significant, the *therapeutic gain is 9.3%*.

Table 9-3 Response rates for alternative responder definition ≥3 CSBM per week (ITT population)

	Tegaserod 2 mg bid N = 417	Tegaserod 6 mg bid N = 431	Placebo N = 416
≥3 CSBM/week, Weeks 1-4			
N (%) responders	77 (18.8)	95 (22.2)	53 (12.9)
Odds ratio (95% CI)	1.66 (1.07, 2.58)	2.28 (1.48, 3.51)	
p-value	0.0249	0.0002	
≥3 CSBM/week, Weeks 1-12			
N (%) responders	70 (17.1)	108(25.2)	59 (14.3)
Odds ratio (95% CI)	1.21 (0.79, 1.85)	2.25 (1.49, 3.38)	
p-value	0.3908	0.0001	

Most of the patients perceived marked improvement in the number of stools per week. Stool characteristics, percentage of SBM with a sensation of complete evacuation, and bothersome bowel habits, abdominal discomfort/pain, and abdominal distention/bloating were the relevant secondary efficacy data gathered from patients' daily diaries. Among the patients treated in Study 2301, the 12 week diaries did not reveal a significant difference between placebo and the 6 mg teg in the percentage of bowel movements with a sensation of "*complete*" evacuation; patient perception of *completeness* being the qualifying assessment for relief of constipation added by Novartis. Although there was improvement from baseline in relief of abdominal symptoms, the

difference between placebo and the tegaserod in the mean (%) weekly improvement was not significant.

2. Study 2302. Relevant Efficacy Results.

Differences between the tegaserod 6 mg bid doses and placebo noted in Study 2301 were replicated in Study 2302. For the primary efficacy endpoint, the therapeutic gain for either tegaserod dose relative to placebo was *15-17%* during the first 4 weeks. The average CSBM/week remained stable over the 12 week study period and was significantly higher for both tegaserod doses relative to placebo. Notable is the absence of dose response observed in this study compared to Study 2301. The response rate for the 2 mg teg group was just over 40%, persisted during the study, and was basically similar to the response rate depicted in the 6 mg teg group. The results during the first month are shown in the next Novartis Table 9-1.

Table 9-1 Primary efficacy variable: Response rate for Complete Spontaneous Bowel Movements during Weeks 1-4 (ITT patients)

Statistic	Tegaserod 2 mg bid N = 450	Tegaserod 6 mg bid N = 451	Placebo N = 447
N	444	449	442
Number (%) of responders	184 (41.4)	194 (43.2)	111 (25.1)
Odds ratio	2.26	2.48	
95% CI for odds ratio	(1.67, 3.05)	(1.84, 3.34)	
p-value	<0.0001	<0.0001	

A responder was defined as a patient who had a mean increase of ≥1 CSBM/week during the first 4 weeks of treatment compared to baseline with a treatment duration of at least 7 days.

As in study 2301, the therapeutic gain for tegaserod decreased markedly if responders were defined by the absence of constipation (=3BM/week). The response rate for the 6 mg teg treatment group went down to *21.5%*, and the therapeutic gain over placebo narrowed to *8.9%* (*see next Novartis Table 9.4*). Again, no dose response was noted.

Table 9-4 Response rates for alternative responder definition of **≥3 CSBM** per week (ITT patients)

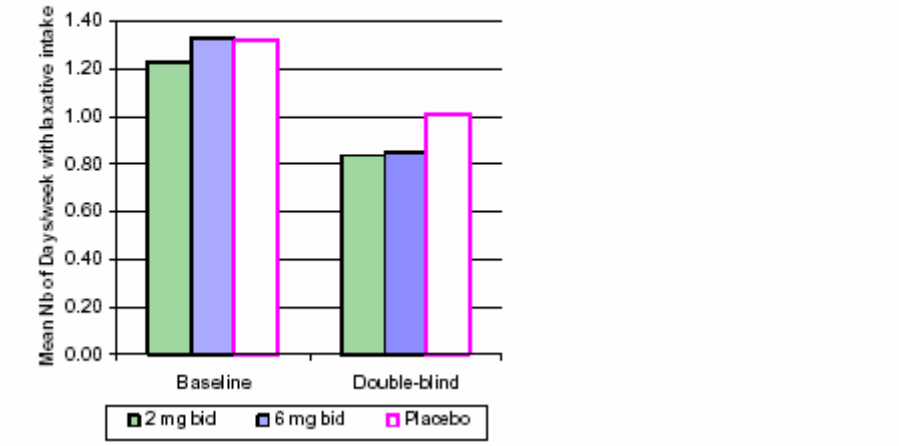
	Tegaserod 2 mg bid N = 450	Tegaserod 6 mg bid N = 451	Placebo N = 447
≥3 CSBM/week			
Weeks 1-4			
N (%) responders	102 (23.0)	98 (21.8)	57 (12.9)
Odds ratio (95% CI)	2.63 (1.75, 3.95)	2.29 (1.52, 3.46)	
p-value	<0.0001	<0.0001	
Weeks 1-12			
N (%) responders	101 (22.7)	99 (22.0)	58 (13.1)
Odds ratio (95% CI)	2.46 (1.66, 3.65)	2.21 (1.49, 3.29)	
p-value	<0.0001	<0.0001	

Analyses of secondary endpoints were favorable to the 6 mg tegaserod group relative to placebo.

3. Use of Rescue Laxative Use.

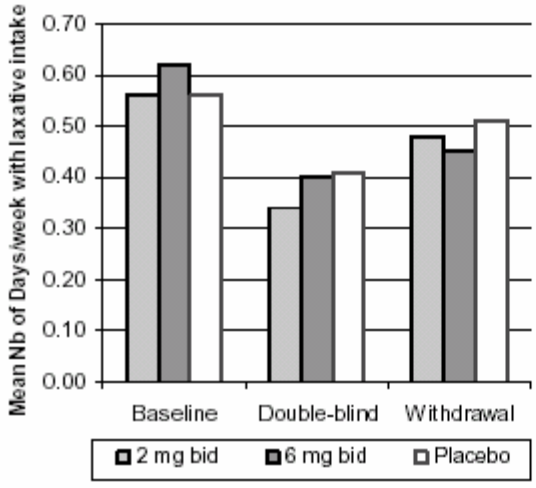
According to the protocol, investigators were allowed to administer bisacodyl tablets as rescue laxative to patients who had a period of 4 days without BMs. This 4 day period was not adhered to in Study 2301. In this study, patients were given the rescue laxative after a period of 3 days without BMs. In both trials, laxative use was higher during baseline than the double-blind period. However, during the double-blind period, 50-58% of patients treated in Study 2301 used rescue laxative sometime during the trial. The proportion of patients who used the rescue laxative was higher in Study 2302, 60-64%. In Study 2301, placebo patients had a significantly higher mean number of days of laxative consumption compared to tegaserod –treated patients, though the difference was not significant, as shown in the next figure (*Novartis Figure 8-1*).

Figure 8-1 **Mean number of days with laxative intake (for patients who took laxatives) by study period (ITT population)**



The difference in laxative use between the tegaserod doses and placebo observed in Study 2301, was not replicated in Study 2302. As seen in the next Novartis Figure 8-1, the mean number of days that patients used the laxative bisacodyl, was similar in the tegaserod and placebo treatment groups.

Figure 8-1 Mean number of days with laxative intake by study period (ITT patients)



C. Reviewer Comments.

This reviewer acknowledges Novartis analyses and results. The submitted studies include fundamental deficiencies related to study design, including issues regarding patient representation and choice of primary efficacy endpoint, and issues regarding the clinical significance of the results. These issues are the topics of discussion included in my next comments.

1. *Patient Representation for the Proposed Indication*.

The prospective study protocol defined the aim for conducting the trials, i.e., *to demonstrate the effect of tegaserod on bowel habits in patients suffering from chronic idiopathic constipation*. The large epidemiological constipation study conducted in the USA (EPOC) defined the subtypes of constipation: functional or idiopathic, IBS-C, and outlet obstruction (outlet) or slow-peristalsis constipation. Idiopathic or functional constipation, encompassing the largest subtype, is almost equally distributed among males and females, and actually represents the most common subtype among men[6]. The population studied by Novartis, *86-92% women, mean age of 46-47 years*, does not appear to represent functional or idiopathic constipation, and strongly suggests a population largely comprised of IBS-C, outlet obstruction or slow peristalsis patients.

Inclusion of patients with IBS-C appears to be corroborated by the history of symptoms. The *main* constipation complaint suffered by up to 30% of enrolled patients was abdominal distention/bloating and abdominal pain was reported by 15% (*see next Novartis Table 7.6-1, Study 2301*). The proportion of subjects reporting such symptoms was similar for Study 2302. Although abdominal pain, abdominal distention and bloating may be present in idiopathic constipation, they are rarely *main* complaints. The

Rome Criteria, universally accepted as the criteria for diagnosis of idiopathic constipation, does not include abdominal symptoms.

Post-text table 7.6-1 (Page 1 of 1)
Patient's main constipation complaint in the preceding 6 months, based on background information, by reason and treatment
(All ITT patients)

Number of patients with Main complaint	Tegaserod 2 mg bid N=417 n (%)	Tegaserod 6 mg bid N=431 n (%)	Placebo N=416 n (%)	Total N=1264 n (%)
Abdominal distension/bloating	122(29.3)	128(29.7)	131(31.5)	381(30.1)
Infrequent defecation	69(16.5)	67(15.5)	65(15.6)	201(15.9)
Abdominal pain	62(14.9)	74(17.2)	58(13.9)	194(15.3)
Feeling of incomplete evacuation	60(14.4)	49(11.4)	64(15.4)	173(13.7)
Straining	50(12.0)	58(13.5)	47(11.3)	155(12.3)
Hard stools	53(12.7)	48(11.1)	46(11.1)	147(11.6)
Other	1(0.2)	6(1.4)	5(1.2)	12(0.9)

The lack of exclusion criteria for IBS-C patients allowed enrollment of patients with a prior confirmed diagnosis of IBS, including patients who appeared to meet the criteria of diarrhea-predominant IBS. The next Novartis table revealed that at least 595 patients (23%) enrolled in the two controlled studies had IBS-like symptoms. Included in this group were patients who had a diagnosis of IBS prior to study entry.

Table 3-1 Number of patients selected as IBS-like (pooled analysis, ITT population)

Criteria	Tegaserod 2 mg bid n (%)	Tegaserod 6 mg bid n (%)	Placebo n (%)	Total n (%)
a. Diagnosis of IBS	29 (3.3)	39 (4.4)	21 (2.4)	89 (3.4)
b. Abd. discomfort as their main complaint	108 (12.4)	109 (12.3)	102 (11.8)	319 (12.2)
c. Bothersome abd. discomfort/pain > 0	825 (95.1)	831 (94.2)	819 (94.9)	2475 (94.7)
d. Diarrhea criteria[1]	90 (10.3)	83 (9.4)	84 (9.7)	257 (9.8)
e. Meets criteria c. and d.	89 (10.2)	78 (8.8)	82 (9.5)	249 (9.5)
f. Meets any of the above criteria a, b or e	204 (23.5)	203 (23.0)	188 (21.7)	595 (22.7)

[1] Patients with ≥25% of SBM loose or watery (stool form 6 or 7) or >3 SBM/day for ≥ 25% of days
SBM: spontaneous bowel movement

In this table, Novartis excluded patients who had as their main complaint abdominal distention/bloating and who appeared to have characteristics of either IBS-C or outlet obstruction constipation.

Further assessment of the majority of these young to middle aged women revealed characteristics of patients affected by outlet obstruction or slow transit constipation. The main characteristic of outlet obstruction or slow transit constipation is *severity* of constipation (*one bowel movement per week and weeks with absence of bowel movements*). The examination of baseline frequency of CSBM/week revealed that a total of 1638 patients (63%) randomized to treatments in these studies had shown complete absence of CSBM at baseline (0 CSBM).

2. *The Primary Efficacy Endpoint*.

Analyses of efficacy based on the primary endpoint established in the protocol, i.e., =1 CSBM than at baseline, showed that treatment with 12 mg/d Zelnorm resulted in =13% superiority over placebo. In considering these numbers, we should more closely examine the relevance of the chosen primary efficacy endpoint, as it relates to the definition of constipation. Does the chosen efficacy endpoint encompass relief of constipation (d*efined by =3 CSBM per week*) or does the chosen endpoint simply refer to an increase in one BM/week, *but* without actual relief of constipation? The latter appears to be the case. Taking this a setp further, we examined the proportion of patients exhibiting zero BMs at baseline and declared *responders with an average of just one single bowel movement per week during the initial month of treatment*. *As seen in the comparisons of data below, 13% to 18% of patients were considered responders with an average of one single BM/week during weeks 1-4 of the twelve week study period (analyses performed by the FDA statistician reviewer, Dr. Joy Mele)*. Minimal differences across treatment groups were observed in this exploratory analysis. The relationship between a change from 0 to 1 CSBM/week and symptom improvement is under review.

Study 2301

Increase=1 CSBM/wk. Wks 1-4 for patients with 0 CSBM at baseline

PLA = 13% 34/266
ZEL 2 = 14% 36/253
ZEL 6 = 13% 35/273

Study 2302

Increase=1 CSBM/wk. Wks 1-4 for patients with 0 CSBM at baseline

PLA = 13% 35/274
ZEL 2 = 19% 55/289
ZEL 6 = 18% 51/283

To further ascertain this point, we analyzed the number of weeks, out of the 12 week study period, in which patients were declared responders, and, met the definition of non-constipation, i.e., =3 BM per week. The next table (*prepared by Dr. Joy Mele*) shows that *responders met the definition of complete relief from constipation (=3 BM/week) less than 25% of the twelve week study period*.

Number of Weeks with 3 or More CSBM

	Study 2301			Study 2302		
	PLA n=416	ZEL 2 n=417	ZEL 6 n=431	PLA n=447	ZEL 2 n=450	ZEL 6 n=451
All patients						
Mean (SD)	2.2 (3.3)	2.6 (3.5)	3.2 (3.9)	2.2 (3.2)	3.1 (3.9)	3.3 (3.7)
Median	0	1	1	0	1	2
Range	0-12	0-12	0-12	0-12	0-12	0-12
Completers*						
Mean (SD)	2.4 (3.3)	2.9 (3.7)	3.6 (4.1)	2.5 (3.4)	3.5 (4.0)	3.8 (3.8)
Median	0	1	2	1	2	3
Range	0-12	0-12	0-12	0-12	0-12	0-12
# of wks w/ 3 or more CSBM						
0	52.6%	46.7%	40.2%	51.6%	38.3%	34.8%
1	12.2%	10%	10.9%	10.8%	14.5%	13.6%
2	7.3%	7.3%	6.4%	6.5%	8.2%	5.9%
3	4.6%	6.1%	6.9%	7.1%	5.7%	7%
4	4.6%	5.6%	4.5%	5.1%	3.2%	5.7%
5	3.9%	3.9%	4.0%	3.7%	5.2%	5.4%
6	1.5%	3.7%	3.5%	1.8%	4.3%	6.8%
7	1.7%	3.4%	4.5%	3.0%	2.7%	4.3%
8	2.2%	2.7%	3.1%	2.5%	4.1%	4.3%
9	2.9%	3.4%	3.3%	2.8%	1.6%	2.5%
10	2.4%	1.2%	4.3%	1.2%	3.4%	3.2%
11	1%	2.4%	3.8%	2.1%	3.9%	3.6%
12	3.2%	3.4%	4.7%	1.8%	5%	2.9%

*received study drug treatment for 12 weeks

3. Clinical Relevance.

It has been estimated that between 4 million to 55 million people in the U.S. are affected by constipation[7]. Idiopathic constipation, with almost equal prevalence in men and women appears to be the most prevalent of the subtypes of constipation. Laxatives, whether bulk-forming agents, osmotic products, or stimulants of the intestinal mucosa are easily available OTC. A few, like PEG-3350 and non-absorbable disaccharides, require a physician prescription. The population affected by constipation, in its majority, self-medicate with laxatives. Many of the habitual laxative consumers, become laxative abusers (*as mentioned in Novartis protocol*). In its 2000 technical review, the American Gastroenterological Association (AGA) recommended to initiate the medical treatment of constipation with a slow increase in the content of dietary fiber. If drugs are required, the AGA[8] recommends starting with a saline laxative, such as milk of magnesia. Only later, stimulant drugs or osmotic agents should be added to the therapy. Randomized trials with high fiber diets, or comparing laxatives, have been carried out, albeit many of them, under deficient designs[9]. Trials revealed little difference between laxatives, and modest improvement over placebo[10]. Hence, the wide interest in the results of these tegaserod trials in chronic constipation. Specifically, the Novartis aim was to assess safety and efficacy of tegaserod maleate in idiopathic constipation.

4. Conclusion

At first glance, the results revealed significant therapeutic gain for tegaserod 6 mg over placebo ranging from as high as13% to as low as 9% depending on the methodology applied for analysis. Dose response was shown only in one trial. Careful examination reveals deficiencies in study design, in study execution, and robustness of results. The design of the studies excluded patients considered laxative abusers, and lacked a provision to exclude patients with IBS-C, a subtype of constipation for which tegaserod is already approved for use under prescription. This lack of provision to exclude IBS-C led to contamination of the total enrolled patient population with almost 600 patients who met the criteria of IBS-C (a few of them met the criteria of IBS-diarrhea predominant). In the execution of the studies, men and the elderly were underrepresented (discussed in the draft statistical review in greater detail), and the studied patient population was young or middle age women, 46 years old. A large proportion (=63%) of these women exhibited severe constipation at the run-in baseline period (0 CSBM) coupled with abdominal symptoms. This latter clinical picture is reminiscent of the clinical picture encountered in outlet obstruction or slow transit constipation. It appears, therefore, idiopathic constipation patients, if present, constituted a minority 9379 or only 15%) of enrollees. A further fundamental deficiency in the design, i.e. choice of primary efficacy endpoint, was subsequently manifested in the results. About 18% of patients with 0 CSBM/wk at baseline were declared responders with only 1 CSBM per week. *Responders to treatment were non-constipated for approximately 42% of the 12-week study treatment*.

In acknowledging the favorable statistics toward tegaserod, this reviewer ponders about the clinical significance of these efficacy results, in the lifelong treatment of chronic constipation, and rather pointedly, in the lifelong treatment of idiopathic, outlet obstruction or slow transit constipation.

References

1. American Gastroenterological Association Medical Position Statement: Irritable Bowel Syndrome. Gastroenterology; 112:2118-2119, 1997.

2. Lembo A and Camilleri M. Chronic Constipation. NEJM; 349:1360-1368, 2003.

3. Wald A. Approach to the Patient with Constipation. Pages 894-910, Textbook of Gastroenterology; Ed T. Yamada, 2003.

4. Lennard-Jones JE. Constipation. Pages 181-210, In Sleisenger & Fordtran's Gastrointestinal and Liver Disease; 7th Edition, 2002.

5. Constipation and the Use of Laxatives; www.terrubins.com

6. Epidemiology of Constipation (EPOC) Study in the United States: Relation of Clinical Subtypes to Sociodemographic Features. American J Gastroenterol; 94, 3530-3540, 1999.

7. Everhart JE et al. A longitudinal study of self-reported bowel habits in the United States. Dig Dis Sci; 43:1153-1162,1989.

8. AGA Technical Review on Constipation. Gastroenterology; 119:1766-1778, 2000.

9. Dettmar PW, Sykes J. A Multi-Centre, General Practice Comparison of Ispaghula Husk versus Lactulose and other Laxatives in the Treatment of Simple Constipation. Curr Med Res Opin; 14:227-233, 1998.

10. Jones MP et al. Lack of Objective Evidence of Efficacy of Laxatives in Chronic Constipation. Dig Dis Sci; 47:2222-2230, 2002.

Clinical Summary of Safety

Gary Della'Zanna, D.O., M.S., Division of Gastrointestinal and Coagulation Drug Products

Ann Corken Mackey, R.Ph., M.P.H. and Allen Brinker, M.D., M.S., Division of Drug Risk Evaluation, Office of Drug Safety

I. Background

Zelnorm was first approved in July 2002 for the short-term treatment (4-6 weeks) of women with constipation predominant irritable bowel syndrome (c-IBS). Since approval, several adverse events of special interest have been identified; these include ischemic colitis, rectal bleeding, and serious complications of diarrhea, including hypotension and syncope. In response to post marketing reports, Novartis revised the Zelnorm package insert on April 27, 2004. These revisions included a WARNINGS section about the serious consequences of diarrhea, including hypovolemia, hypotension, and syncope and a PRECAUTIONS section describing ischemic colitis and other forms of intestinal ischemia. In addition to this, Novartis mailed a Dear Health Care Professional Letter outlining these changes (see Appendix 1 and 2).

With the proposed new treatment indication, chronic constipation, and the recent labeling change, the Division is asking the Gastrointestinal Drugs Advisory Committee to discuss the risk:benefit profile of Zelnorm for the proposed indication and to address the adequacy of the labeling for adverse events of special interest. This review will discuss safety data from the constipation clinical trials, from pooled clinical trials, and from postmarketing surveillance.

II. Chronic Constipation Clinical Trials

The chronic constipation studies consisted of two clinical trials (E2301, E2302) lasting 12 weeks each (Key Safety Population) and a long-term extension of study E2301, (E2301E1) lasting an additional 10 months (Key Long-term Safety Population). The type and incidence of adverse events reported during the chronic constipation trials were similar to the c-IBS trials and to what is printed in the current label. Table 1 lists the most frequent adverse events in the chronic constipation trials in the key safety population.

Table 1
Most Frequent Adverse Event (≥ 2% of patients in any group)
Key Safety Population

	Tegaserod 2 mg bid n (%)	Tegaserod 6 mg bid n (%)	Placebo n (%)	Tegaserod any dose n (%)
Patients Studied				
Total no. studied	861 (100)	881 (100)	861 (100)	1742 (100)
Total no. with an AE	485 (56.3)	503 (57.1)	513 (59.6)	988 (56.7)
Adverse Event preferred term				
Headache NOS	87 (10.1)	97 (11.0)	114 (13.2)	184 (10.6)
Nasopharyngitis	44 (5.1)	63 (7.2)	62 (7.2)	107 (6.1)
Diarrhea NOS	36 (4.2)	58 (6.6)	26 (3.0)	94 (5.4)
Abdominal pain NOS	52 (6.0)	41 (4.7)	45 (5.2)	93 (5.3)
Nausea	41 (4.8)	41 (4.7)	32 (3.7)	82 (4.7)
Upper respiratory tract infection NOS	30 (3.5)	31 (3.5)	17 (2.0)	61 (3.5)
Abdominal distension	28 (3.3)	32 (3.6)	30 (3.5)	60 (3.4)
Sinusitis NOS	27 (3.1)	30 (3.4)	20 (2.3)	57 (3.3)
Flatulence	27 (3.1)	25 (2.8)	30 (3.5)	52 (3.0)
Dyspepsia	24 (2.8)	25 (2.8)	26 (3.0)	49 (2.8)
Influenza	24 (2.8)	22 (2.5)	25 (2.9)	46 (2.6)
Back pain	20 (2.3)	25 (2.8)	24 (2.8)	45 (2.6)
Abdominal pain upper	18 (2.1)	16 (1.8)	16 (1.9)	34 (2.0)
Arthralgia	12 (1.4)	18 (2.0)	19 (2.2)	30 (1.7)
Dizziness	8 (0.9)	20 (2.3)	16 (1.9)	28 (1.6)
Urinary tract infection NOS	17 (2.0)	10 (1.1)	6 (0.7)	27 (1.5)
Cough	10 (1.2)	9 (1.0)	20 (2.3)	19 (1.1)

Studies: E2301 and E2302
Source: Post-text table 4.9-1

During the uncontrolled long-term extension study (E2301E1), adverse events followed a similar pattern as seen in the key safety population, although the incidence rates were generally higher. Interestingly, constipation was reported more frequently as an adverse event during long-term extension. Table 2 lists the most frequent adverse events in the chronic constipation trials in the key long-term safety population.

Table 2
Most frequent Adverse Event (≥ 2% of patients in any group)
Key Long-Term Safety Population

	Tegaserod 2 mg bid - 2 mg bid N = 283	Tegaserod 6 mg bid - 6 mg bid N = 283	Placebo - Tegaserod 6 mg bid N = 274	Tegaserod any dose (total) N = 840
Total number (%) of patients with AE(s)	226 (79.9)	215 (76.0)	180 (65.7)	621 (73.9)
Adverse Event preferred term	n (%)	n (%)	n (%)	n (%)
Headache	68 (24.0)	60 (21.2)	44 (16.1)	172 (20.5)
Abdominal pain NOS	42 (14.8)	32 (11.3)	30 (10.9)	104 (12.4)
Diarrhea NOS	23 (8.1)	28 (9.9)	29 (10.6)	80 (9.5)
Nasopharyngitis	27 (9.5)	31 (11.0)	19 (6.9)	77 (9.2)
Nausea	35 (12.4)	26 (9.2)	12 (4.4)	73 (8.7)
Influenza	19 (6.7)	29 (10.2)	16 (5.8)	64 (7.6)
Back pain	17 (6.0)	20 (7.1)	14 (5.1)	51 (6.1)
Abdominal distension	16 (5.7)	22 (7.8)	11 (4.0)	49 (5.8)
Abdominal pain upper	18 (6.4)	19 (6.7)	12 (4.4)	49 (5.8)
Constipation	13 (4.6)	18 (6.4)	11 (4.0)	42 (5.0)
Dyspepsia	21 (7.4)	11 (3.9)	9 (3.3)	41 (4.9)
Flatulence	11 (3.9)	14 (4.9)	16 (5.8)	41 (4.9)
Sinusitis NOS	16 (5.7)	14 (4.9)	6 (2.2)	36 (4.3)
Arthralgia	12 (4.2)	12 (4.2)	7 (2.6)	31 (3.7)
Dizziness	12 (4.2)	15 (5.3)	4 (1.5)	31 (3.7)
Bronchitis NOS	16 (5.7)	8 (2.8)	5 (1.8)	29 (3.5)
Insomnia	7 (2.5)	13 (4.6)	8 (2.9)	28 (3.3)
Cough	10 (3.5)	7 (2.5)	7 (2.6)	24 (2.9)
Respiratory tract infection NOS	10 (3.5)	6 (2.1)	8 (2.9)	24 (2.9)
Pharyngolaryngeal pain	9 (3.2)	6 (2.1)	8 (2.9)	23 (2.7)
Urinary tract infection NOS	8 (2.8)	9 (3.2)	6 (2.2)	23 (2.7)
Depression	5 (1.8)	6 (2.1)	9 (3.3)	20 (2.4)
Migraine NOS	9 (3.2)	7 (2.5)	4 (1.5)	20 (2.4)
Dysmenorrhea	7 (2.5)	5 (1.8)	7 (2.6)	19 (2.3)
Fatigue	5 (1.8)	9 (3.2)	5 (1.8)	19 (2.3)
Pharyngitis	4 (1.4)	10 (3.5)	5 (1.8)	19 (2.3)
Chest pain	10 (3.5)	5 (1.8)	3 (1.1)	18 (2.1)
Vomiting NOS	7 (2.5)	10 (3.5)	1 (0.4)	18 (2.1)
Vertigo	9 (3.2)	5 (1.8)	3 (1.1)	17 (2.0)

Adverse events are sorted by descending order of incidence in the combined tegaserod groups.

Studies : E2301E1 (including periods of tegaserod exposure during E2301)
Source: [CSR E2301E1 Post-text table 10.1-8]

This safety review will focus on selected adverse events of special interest. The review will include post-marketing data and the safety data from the chronic constipation trials, as well as pooled data from 33 additional clinical trials for other indications (Pooled Indication Population).

III. Drug Use*

IMS Health (projected data): There were a total of ---------- prescriptions for tegaserod 6 mg and ---------- prescriptions for tegaserod 2 mg dispensed by retail pharmacies (chain, independent, food stores, and mail order) in the U.S from August 1, 2002 through April 30, 2004. The chart below depicts quarterly totals of prescriptions dispensed (tegaserod 2 mg and 6 mg combined). (Drug use data for August 2002 was minimal and is not included in the chart.)

Drug Use Demographics[†]

---

* Drug use data provided by Yoon Kong, Pharm.D., Drug Utilization Specialist, Division of Surveillance, Research and Communication Support, ODS.

[†] Projected data per IMS. Note that prescriber specialty data represent the August 2002 through April 2004 time period; indication for use data and gender/age data represent the August 2002 through March 2004 time period.

IV. Adverse Events of Special Interest

The Adverse Event Reporting System (AERS) is a passive surveillance system that is subject to under-reporting; normally only 1 to 10% of adverse events are reported to FDA (Physician knowledge, attitudes, and behavior related to reporting of adverse drug events. Arch Intern Med 1998; 148: 1596-1600 and Rhode Island physicians' recognition and reporting of adverse drug reactions. R I Med J 1987; 70: 311-6).

The post-marketing cases discussed in this document were reported through the Adverse Event Reporting System (AERS) between the initiation of marketing in the US in August 2002 through April 15, 2004. The applicant's data lock point was March 31, 2004, so the April 15 date allows for the applicant's reports to be received and processed by the agency. Note that a paragraph in section B (Ischemic Colitis and Rectal Hemorrhage) discusses cases of ischemic colitis and intestinal ischemia received between April 15 and June 1, 2004. These reports were included in order to capture reports subsequent to dissemination of the Dear Health Care Professional letter by the sponsor on April 26, 2004.

When evaluating spontaneous reports, it is important to keep the following limitations in mind. The main utility of a spontaneous reporting system, such as AERS, is to detect signals of potential drug safety issues that are rare. It should be realized that accumulated case reports cannot be used to calculate incidence or estimates of drug risk for a particular product because under-reporting of adverse events exists. Some of the factors that influence reporting include the length of time a drug is marketed, the market share, size and sophistication of the sales force, publicity about an adverse reaction and regulatory actions. It should also be noted that in some of these cases, the reported clinical data were incomplete, and there is no certainty that these drugs caused the reported reactions. A given reaction may actually have been due to an underlying disease process or to another coincidental factor.

Some of the reports received through AERS were submitted by patients; in general the quality and completeness of the data are not as good as reports received from health care professionals. ODS has included these reports in our analysis because the actual occurrence of these events could not be ruled out. The absence of supporting documentation does not imply that the patient did not have the event, only that documentation was not obtainable.

A. Fatalities

As of April 15, 2004, there were a total of 22 deaths from all causes in patients receiving tegaserod in AERS (note that some of these cases also are included in the Ischemic Colitis and Rectal Hemorrhage section

below). This number represents unduplicated patient cases, not individual reports. The cases are described below.

Causes of death (mutually exclusive)
Total (n=22)

Sepsis related to ischemic bowel disease (n=1)
Bowel infarction/peripheral vascular disease (n=1)
Intestinal gangrene/bowel perforation (n=1)
Intestinal ischemia (n=1)

Other causes (n=18) (e.g., cardiac arrest, suicide, coma/diabetic neuropathy, bulbar palsy, renal failure, MI, bowel impaction, complications of anorexia, cancer)

Eighteen of the patients were female and four patients were male, ranging in age from 32 to 90 years, with a mean age of 67 years. These patients were taking tegaserod for the following indications: IBS constipation predominant (7), IBS predominance not specified (2), IBS alternating predominance (2), constipation (6), paralytic ileus (1), and unknown indication (4).

B. Ischemic Colitis and Rectal Bleeding

1. Post-Marketing Surveillance

Ischemic colitis, and other forms of intestinal ischemia, were identified as adverse events of special interest. The first reported post-marketing case of intestinal ischemia in a patient receiving Zelnorm was identified by the Office of Drug Safety (ODS) in March 2003, when a search of the Adverse Event Reporting System (AERS) database for rectal bleeding was performed.

As of April 15, 2004, the Agency received 20 reports of ischemic colitis and 4 reports of intestinal ischemia through AERS. The definition used by ODS to identify potential cases of ischemic colitis for epidemiological risk assessment was based on either of the following: (1) the term ischemic colitis was explicitly used in the AERS report as a possible diagnosis, or (2) any endoscopic or histologic evidence of ischemic change or necrosis. The search criteria were extended to include other forms of intestinal ischemia. The definition for intestinal ischemia included cases where an occlusive process of the proximal large vessels of the bowel was suggested.

A summary of the ischemic colitis and intestinal ischemia cases is provided in Appendix 3. Of the 20 cases of ischemic colitis, 19 were

female, ranging in age from 26 to 82 years, with a mean age of 55. The majority of the patients were treated for IBS constipation predominant (n=10), IBS predominance unspecified (5), and IBS alternating predominance (1). The remaining four patients were treated off label [constipation (n=2), postoperative ileus (n=1), unknown indication (n=1)]. Five of the 20 reported cases of ischemic colitis had no documented risk factors. The remaining 15 patients had one or more identifiable risk factors (i.e., hormone therapy, tobacco use, and vascular disease). Three of the 20 reported cases occurred on the first day of therapy, with two of the three cases occurring in patients with no known risk factors. The other times to onset were: 2 to 20 days (6), 21 to 122 days (7), 230 to 398 days (3), and unknown (1). Thirteen of the 20 patients required hospitalization (with one of these thirteen required surgery) and one died.

The four cases defined as intestinal ischemia included the following diagnoses: intestinal ischemia (n=1), intestinal gangrene (n=1), mesenteric ischemia (n=1), and abdominal compartment syndrome with intestinal ischemia (n=1). All patients were female, ranging in age from 41 to 67 years. Three of the patients were treated for IBS; one was treated off label for constipation. The times to onset were 6, 56, and 105 days (1 case unknown). Three patients were treated with surgery. One patient required a bowel resection; the other two had exploratory laparotomies. Three of the four patients died.

The majority of these cases have been adjudicated with Novartis and for the most part there is agreement that the cases represent some form of bowel ischemia. Many of the post-marketing cases of ischemic colitis and intestinal ischemia had confounding factors that may have contributed to the development of intestinal ischemia. Of the 20 cases of ischemic colitis, six were receiving hormonal therapy, which can be associated with vascular thrombosis and coagulopathies. Several had complicated medical histories.

ODS has received 7 cases of ischemic colitis, 1 case of bowel infarction, and 1 case of ischemic colitis secondary to small vessel ischemia from April 15, 2004 through June 1, 2004 (ODS is waiting for additional information on some of these cases). All 9 patients were female, ranging in age from 31 to 78 years, with a mean age of 45 years. The patients were treated for the following indications: IBS constipation predominant (3), IBS predominance unspecified (2), IBS alternating predominance (1), constipation (1), “bloating” (1), and unknown indication (1). They were receiving the following daily doses: 4 mg (1), 6 mg (2), 12 mg (3), 6 mg every other day (1), and unknown (2). Times to onset were: 1 to 8 days (3), 16 to 41 (3), and 156 to 293

(3). Three of the seven patients had risk factors (i.e., marathon running [1] and vascular disease [2]). Six patients required hospitalization, with one of those patients requiring a small bowel resection.

Rectal bleeding was also analyzed using the post-marketing data and the safety data from the current application. Rectal bleeding is difficult to assess using post-marketing data. Spontaneous reporting systems are designed for detection of rare and serious adverse events. The definition for epidemiological risk assessment included any AERS report using the terms rectal bleeding, rectal hemorrhage, bloody stool, hematochezia, lower gastrointestinal bleeding, or melena.

As of April 15, 2004, ODS received 40 AERS reports of rectal bleeding (note: cases of rectal bleeding resulting from other processes [e.g., inflammatory bowel disease, and ischemic colitis] have been excluded from this number). The quality of the information for many of the reports was poor. Fourteen (35%) reports were submitted by patients, most of which provided very little information.

Almost half of the post marketing cases of rectal bleeding (n=19) originated from foreign sources. Eighteen (18) of the 40 cases had diagnostic workups that demonstrated the following: normal exam (n=9), hemorrhoids (n=2), polyp and hemorrhoids (n=1), rectal irritation (n=2), diverticulum (n=3), and angiodysplasia (1).

2. Clinical Trials

A thorough review of the safety data from the chronic constipation trials did not identify any cases suspicious of ischemic colitis. The incidence and severity of rectal bleeding in the key safety population were balanced across treatment groups (Table 3). Two patients discontinued from the study due to rectal bleeding, one in the placebo group and one in the tegaserod 2 mg BID group.

Table 3

Gastrointestinal Bleeding Key Safety Population				
	Tegaserod 2 mg bid (N=861)	Tegaserod 6 mg bid (N=881)	Placebo (N=861)	Tegaserod Any dose (N=1742)
GI bleeding and Related Symptoms	10 (1.2)	10 (1.1)	11 (1.3)	20 (1.1)
Rectal hemorrhage	5 (0.6)	6 (0.7)	5 (0.6)	11 (0.6)
Blood in stool	3 (0.3)	3 (0.3)	5 (0.6)	6 (0.3)
Anal hemorrhage	0	1 (0.1)	0	1 (0.1)
Gastrointestinal hemorrhage NOS	1 (0.1)	0	0	1 (0.1)
Melena	1 (0.1)	0	0	1 (0.1)
Occult blood NOS positive	0	0	1 (0.1)	0
Discontinuations due to GI bleeding	1 (0.1)	0	1 (0.1)	1 (0.1)
(Ref: Table 8-3 Summary of Clinical Safety)				

As part of the safety review for the present application, the Division also reviewed the safety data from completed trials of similar design. This review included the original IBS application and safety data from completed studies through September 2003. This database included over 12,000 patients in randomized trials. To identify potential cases of bowel ischemia, these data were analyzed by the Novartis, at the request of the Division, using search criteria for all forms of rectal bleeding that resulted in any diagnostic work-up or therapeutic intervention (endoscopy or x-ray). A detailed review of the case report forms and source data from this search did not identify a case that appeared suspicious for ischemic colitis.

C. Diarrhea

1. Post-Marketing Surveillance

The current label states that diarrhea was reported as an adverse event in 9% of the patients receiving Zelnorm during the IBS trials, compared to 4% in the placebo group. During the post-marketing period, ODS received 22 AERS reports of serious complications of diarrhea. The definition for epidemiological risk assessment was diarrhea or suspected diarrhea that led to an ER visit, serious outcome (i.e., death, life-threatening, hospitalization), or complications, including but not limited to, dehydration, hypokalemia, and/or the need for intravenous fluid replacement (note: cases of serious

diarrhea were excluded from this analysis if the diarrhea was caused by another process [e.g., infection]).

Of the 22 cases of serious complications of diarrhea, 20 were reported by health care professionals and two were reported by the consumer. Consistent with prescribing patterns, the majority of the cases occurred in female patients (Female=20, Male=2). These patients ranged in age from 24 to 82 years (Median=59, Mean=56). Patients were taking the following daily doses: 6 mg (3), 12 mg (13), 6 mg tapered to 2mg (1), and dose unspecified (5). Times to onset were: 1 day (5), 2 to 7 days (6), 21 days (1), 72 to 210 days (4), and unknown (6). In addition to diarrhea, the complications included the following (not mutually exclusive): dehydration (n=12), abdominal pain (n=8), hypotension (n=3), hypokalemia (n=2), nausea/vomiting (n=3), hyponatremia (1), hypothermia/shock (n=1), atrial flutter/fibrillation (n=1), hypovolemic shock/loss of consciousness (n=1). Fifteen of the cases of diarrhea required hospitalization and three were described as life threatening.

2. Clinical Trials

During the chronic constipation trials the frequency and severity of diarrhea were dose-related (Table 4). Four percent of patients in the tegaserod 2 mg b.i.d. group and 7% of patients in the 6 mg b.i.d. group reported diarrhea as an adverse event. Diarrhea was reported as an adverse event in only 3% of the patients in the placebo group. Diarrhea was reported as severe in three patients in the tegaserod 2 mg b.i.d. group, 7 patients in the 6 mg b.i.d. group and 2 patients in the placebo group.

Table 4

Diarrhea Chronic Constipation Trials Key Safety Population									
Preferred Term	**Tegaserod 2 mg bid (N=861)**			**Tegaserod 6 mg bid (N=881)**			**Placebo (N=861)**		
Diarrhea Symptoms	**36 (4.2)**			**58 (6.6)**			**26 (3.0)**		
Diarrhea resulting in medication permanently discontinued	**3 (0.3)**			**8 (0.9)**			**2 (0.2)**		
Severity of Diarrhea	**mild**	**mod**	**sev**	**mild**	**mod**	**sev**	**mild**	**mod**	**sev**
	16	**17**	**3**	**25**	**26**	**7**	**11**	**13**	**2**
(Ref: Table 4-4 Summary of Clinical Safety) Severity rating: mild, moderate (mod), severe (sev)									

The chronic constipation trials enrolled a total of 213 (12.2%) patients ≥ 65 years of age (Table 5). For the proposed dose, patients 65 years and older had a higher incidence of diarrhea (12.5%) and discontinuations due to diarrhea (3.4%) than patients younger than 65 years of age [diarrhea (5.9%), discontinuations due to diarrhea (0.6%)]. This is relevant considering the potential number of elderly people who may be treated for constipation.

Table 5

Diarrhea Chronic Constipation Trials Patients [3] 65 Years			
Preferred Term	**Tegaserod 2 mg bid (N=125)**	**Tegaserod* 6 mg bid (N=88)**	**Placebo (N=117)**
Diarrhea Symptoms	**4 (3.2)**	**11 (12.5)**	**2 (1.7)**
Diarrhea resulting in medication discontinued	**0 (0.0)**	**3 (3.4)**	**1 (0.9)**
(Ref: Table 4-17 Summary of Clinical Safety) *proposed dose			

There was also an increased incidence of diarrhea during the long-term extension portion of the study. Diarrhea was reported in 9.5% of patients receiving tegaserod during the long-term extension, compared to 6.6% in the core part of the study lasting 12 weeks (Tegaserod 6 mg bid group). Although this is similar to what is reported in the label, it is relevant considering the indication is for chronic therapy and the potential number of elderly people that will be treated for constipation chronically.

In the pooled indication population, the frequency of diarrhea was analyzed by treatment indication (Table 6). The incidence of diarrhea was similar to the current label (10%) in patients treated for a lower GI indication. The incidence was much higher in patients treated for an upper GI indication in other clinical trials (22%).

Table 6

Diarrhea Pooled Indication Population		
Study Indication	**Tegaserod %(n/N)**	**Placebo %(n/N)**
Lower GI Indication	**9.93 (568/5721)**	**3.89 (137/3523)**
Upper GI Indication	**21.61 (247/1143)**	**9.95 (39/392)**
All Indications	**11.87 (815/6864)**	**4.50 (176/3915)**
(Ref: Post-text table 4.27-5 and 4.27-7)		

D. Hypotension

1. Post-Marketing Surveillance

As part of the recent labeling changes, hypotension is now listed in the WARNINGS section of the current label as one of the serious complications of diarrhea. During the post-marketing period, the ODS received 15 AERS reports of hypotension. Many of these cases were confounded by underlying medical conditions (i.e., myocardial infarction, drug allergy, and small bowel obstruction). Hypotension was reported in three of the cases of serious complications of diarrhea and in two of the cases of ischemic colitis.

2. Clinical Trials

The development of hypotension may not be limited to complications of diarrhea. During Phase I development of Zelnorm, rare cases of hypotension were reported in healthy subjects. Because of this, Phase II and Phase III studies paid close attention to the effects of tegaserod on blood pressure and pulse. In the c-IBS trials, adverse events suggestive of orthostatic hypertension were reported with similar frequency in the placebo and tegaserod groups. The most common adverse event suggestive of orthostatic hypertension was dizziness, which had a similar frequency in all the treatment groups. However, syncope was more frequent in the tegaserod group compared with the placebo group (0.5% vs. 0.1%) p=0.16.

In the chronic constipation trials, orthostatic hypotension was defined as a reduction in systolic blood pressure of at least 20 mm Hg or a reduction in diastolic blood pressure of at least 10 mm Hg immediately after standing (or 3 min after standing) compared to the measurements taken in the sitting position. The incidence of orthostatic hypotension in the key safety population was balanced across treatment groups with no appreciated dose relationship. Orthostatic hypotension occurred in 14.6% of patients on tegaserod 2 mg b.i.d., 10.9% on tegaserod 6 mg b.i.d. and 12.0% on placebo.

E. Syncope

1. Post-Marketing Surveillance

As part of the recent labeling changes, syncope is now listed in the WARNINGS section of the current label as one of the serious complications of diarrhea. As of April 15, 2004, ODS received eight post-marketing reports of syncope/loss of consciousness. Most of those patients had other factors

that may have contributed to the events; however, the role of tegaserod could not be completely ruled out.

2. Clinical Trials

In the chronic constipation trials, Novartis reports that none of the severe cases of diarrhea developed syncope. During the c-IBS trials the incidence of syncope was low, but it was more frequent in the tegaserod group compared with the placebo group (0.5% vs. 0.1%) p=0.16.

F. Abdominal and Pelvic Surgery

1. Post-Marketing Surveillance

At the time of the original approval, there were questions about whether the use of tegaserod resulted in an increase in abdominal and pelvic surgery. Between August 2002 and April 15, 2004, ODS received 28 AERS reports of patients who experienced adverse events involving the gallbladder while receiving tegaserod. The definition for epidemiological risk assessment was any case reported as cholecystectomy, cholelithiasis, or cholecystitis. Of the 28 reported cases involving the gallbladder, five were excluded from analysis for the following reasons: cholecystectomy planned before tegaserod therapy initiated (n=4) and one patient had a cholecystectomy while having a colon resection for colon cancer. For the remaining 23 cases, 6 had very little information (e.g., medical history, concomitant medications) and 8 had a prior history of gallbladder disease.

During the same period, ODS received 13 AERS reports of patients who experienced adverse events involving the ovary or fallopian tube. The definition for epidemiological risk assessment was any adverse event reported as ovarian or fallopian tube cyst or ovarian surgery. Five reports were excluded for the following reasons: underlying ovarian cancer (n=3); underlying colon cancer leading to removal of gall bladder, ovaries, and colon (n=1); and patient had pain "suggestive" of ovarian cyst rupture 3 months after tegaserod was discontinued (n=1). For the eight remaining cases, the adverse events were reported as: ovarian cyst (7), hematosalpinx cyst (n=1), oophorectomy (n=1), hysterectomy (n=1) (not mutually exclusive).

2. Clinical Trials

In the original application nine cases of ovarian cysts were reported. Eight of the nine cysts were in tegaserod-treated patients; only one occurred in the placebo group. Five of the eight cases required surgery, all from the

tegaserod group. There was also an imbalance in the number of cholecystectomies performed in Zelnorm-treated patients [Zelnorm (5/2,965; 0.17%) vs. placebo (1/1,740; 0.06%)], this difference was not statistically significant. To determine whether the use of tegaserod resulted in an increase in abdominal and pelvic surgery, Novartis created an adjudication board consisting of independent consultants with expertise in IBS, GI motility, and evidence-based medicine. This board reviewed all surgeries in a blinded manner.

The number of abdominal and pelvic surgeries performed during the chronic constipation trials were too small to identify an imbalance. In the key safety population, the incidence of any abdominal and pelvic surgeries in tegaserod-treated patients was lower than in the placebo group [Zelnorm 0.5% (9 cases), Placebo 0.9% (8 cases)]. Only one cholecystectomy was reported in the key safety population. This occurred in a patient receiving tegaserod 6 mg b.i.d.

Six patients (0.7%) in the key long-term safety population required abdominal/pelvic surgery (non-placebo-controlled study). Two of these surgeries were for removal of ovarian cysts; one was detected on day 1 of the extension period. Prior to enrolling in the extension study, this patient was in the placebo group during the core trial. The other case occurred in a patient treated with tegaserod and was detected during the core period and removed on day 5 of the extension study. The other four surgeries occurred between 210 and 392 days after start of the extension phase and included an inguinal hernia repair in the tegaserod 2 mg b.i.d. group, one hysterectomy and curettage due to increased menorrhagia in the tegaserod 6 mg group, and bladder surgery to correct a preexisting urinary stress incontinence and an appendectomy in the placebo-tegaserod 6 mg b.i.d. group.

In the pooled indication population, 27 surgeries were adjudicated in a blinded fashion by the independent board and were judged to be unrelated to study drug and were excluded from analysis [Tegaserod (n=15), Placebo (n=12)]. Three cases in the tegaserod group were not adjudicated because they were identified after the review. These cases were included in the number of cases defined as possibly related to study drug. Table 7 lists the frequency of abdominal and pelvic surgeries in the pooled indication population and shows the results of the independent board's assessment.

Table 7

Frequency of Abdominal and Pelvic Surgeries Pooled Indications Population Placebo-Controlled Trials					
Population	**Tegaserod (N = 6864)**	**Placebo (N = 3915)**	**Treatment Difference (95% CI)**	**p-value**	**Relative Risk (95% CI)**
All cases	**0.42% (29 cases)**	**0.41% (16 cases)**	**0.01 (-0.24, 0.27)**	**0.790**	**1.08 (0.60, 1.97)**
Cases adjudicated as unrelated to study drug	**15 cases**	**12 cases**			
Cases adjudicated as at least possibly related to study drug.	**0.20% (14 cases)**	**0.10% (4 cases)**	**0.10 (-0.04, 0.25)**	**0.206**	**2.08 (0.65, 6.61)**
Uncontrolled trials All cases	**N = 4614 0.72% (33 cases)**	**NA**			
Frequency corresponds to number of patients with surgeries (including cholecystectomies)/number of patients treated. The p-value was calculated using the Mantel-Haenszel test. (Ref. Post-text tables 4.26-1, 4.26-3, 4.26-5)					

The incidence of abdominal and pelvic surgeries was comparable across treatment arms. However, a higher proportion of surgeries in the tegaserod group was adjudicated as at least possibly related to study drug.

As described earlier, only one cholecystectomy was reported in the chronic constipation trials. In the pooled indication population, the frequency of cholecystectomy (all cases) was higher in the tegaserod group than in the placebo group [Tegaserod 0.12% (8/6864), Placebo 0.03% (1/3915). Novartis calculated exposure-adjusted frequency of unadjudicated and adjudicated cholecystectomies (Table 8).

The blinded adjudication excluded four cases of cholecystectomy from the analysis of risk of cholecystectomy (all in the tegaserod group); this resulted in a smaller difference between groups (0.06% on tegaserod vs. 0.03% on placebo). Also, in the pooled indications population the frequency of hepatobiliary disorders reported as serious adverse events was higher in the tegaserod group (0.09% (6/6864)) compared to placebo (0.03% (1/3915)).

Table 8

Cholecystectomy Incidence in Placebo-controlled Trials Pooled Indications Population					
	Treatment	**% (n/N)**	**Exposure (Days)**	**Estimated Frequency Per 100 patient-years exposure**	**p-value vs placebo**
All cases	**Tegaserod**	**0.12 (8/6864)**	**491402**	**0.59 (0.18, 1.01)**	**0.111**
	Placebo	**0.03 (1/3915)**	**284777**	**0.13 (0.00, 0.38)**	
Cases adjudicated as related	**Tegaserod**	**0.06 (4/6864)**	**491402**	**0.30 (0.01, 0.59)**	**0.438**
	Placebo	**0.03 (1/3915)**	**284777**	**0.13 (0.00, 0.38)**	
Cases adjudicated as unrelated	**Tegaserod**	**4 / 6864**			
	Placebo	**0 / 3915**			
Uncontrolled Trials	**Tegaserod**	**0.13 (6/4614)**	**770215**	**0.28 (0.06, 0.51)**	

(Ref: Table 4-16 Summary of Clinical Safety)
Frequency corresponds to number of patients with cholecystectomies/number of patients treated.
The p-value was calculated using the Mantel-Haenszel test and refers to the exposure-adjusted frequency.

These data are difficult to interpret. It is uncertain how adjudicated cases were handled. It is generally accepted that approximately 10% of the adult population have cholelithiasis, but less than half of these patients develop symptoms.

III. CONCLUSIONS

The chronic constipation trials did not identify any new safety concerns, and the incidence and type of adverse events were similar to what is already included in the current label. Many of the Division's safety concerns that were identified during the post-marketing period have been addressed with the inclusion of serious consequences of diarrhea in the WARNINGS section of the label and ischemic colitis and other forms of intestinal ischemia in the PRECAUTIONS section (Appendix 1).

The Agency is seeking the committee's advice about whether ischemic colitis and other forms of intestinal ischemia should be moved to the WARNINGS section of the package insert. The regulations [21 CFR 201.57(e)] state that "The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." Seven of the 20 cases of ischemic

colitis presented were less than 49 years of age, with two of the patients aged 20 and 29 years. Five of the 20 reported cases had no documented risk factors. Three cases occurred on the first day of therapy, with two of the three cases occurring in patients with no reported risk factors.

The appearance of ischemic colitis in young patients, in close temporal association with the drug is concerning. Ischemic colitis is generally considered a disease of the elderly. A recent study reported that the crude, age-stratified incidence of ischemic colitis differ by two orders of magnitude between the youngest strata [0.5 per 100,000 person years in individuals aged <20 years] and the oldest [97 per 100,000 person-years for individuals aged 70-79 years] (Occurrence of colon ischemia in relation to irritable bowel syndrome. Am J Gastroenterol 2004;99(3):486-91). Thus, the appearance of ischemic colitis in association with tegaserod in young patients is unexpected. This suggests, but does not prove, that tegaserod caused the ischemic colitis. Reports of IC in older patients could be attributed to the elevated rate of IC in that segment of the population or to misdiagnosis. Further accumulation of case reports such as these, including reports of clinical severity (i.e., hospitalization, surgery, death) may suggest that the Agency consider new labeling for tegaserod to exclude organic diseases that mimic IBS.

Novartis believes that there is no causal relationship between the use of Zelnorm and the development of ischemic colitis. It is their position that there is already a higher background incidence of ischemic colitis in IBS patients. To support this position, Novartis references a claims data study describing a higher incidence of ischemic colitis in IBS patients. According to Novartis' interpretation of the data, Zelnorm's post-marketing report rate is actually lower than the anticipated background rate. They also reference a study by the American Society of Gastrointestinal Endoscopy that reports the background rate of ischemic colitis in the general population, found during asymptomatic screening, as 20/100,000 patients. Novartis reports the incidence of ischemic colitis in patients treated with Zelnorm as 6/100,000. The Division has requested the complete ASGE study report to review.

After reviewing the available data, it appears that the data supporting an association between ischemic colitis and IBS may be attributable to the significant limitations in the assessment and classification of ischemic colitis based on ICD9 codes. The studies employed the ICD9 code 564.1 (irritable colon) as a surrogate for a diagnosis of IBS, as there is no unique ICD9 code that is limited to ischemic colitis alone. In review of data submitted for the re-evaluation of alosetron, a strong temporal association was found between the index appearance of ICD9 code 564.1 within patient records and a follow-up (subsequent) diagnostic claim for ischemic colitis. This suggests ICD9 code 564.1 may have been an interim diagnosis or in some instances a misdiagnosis. Therefore, there does not appear to be compelling evidence to suggest that a

clinically robust diagnosis of IBS is associated with any increased risk for ischemic colitis in comparison to age-matched peers.

There were no cases of ischemic colitis observed in the clinical trials. An analysis of patients randomized to tegaserod among placebo-controlled trials of at least 3-months duration (n=7,000) was performed by the Agency. Based on application of a Poisson distribution, this would suggest, with 95% confidence, that ischemic colitis occurs no more frequently in the population studied than approximately 1 in 2,000. While this estimate could be viewed by some as too high given the large utilization/exposure of tegaserod, it should be noted that patients in clinical trials were subjected to inclusion, exclusion, and follow-up criteria that are not applicable to general clinical practice. On average, the patients with ischemic colitis as reported to FDA, are both older and carry more co-morbid conditions than those in the tegaserod clinical trials. Thus, generalizabilty of a rate, even an upper bound, for tegaserod-associated ischemic colitis from clinical trials to the population at large is problematic.

Novartis also states that no mechanism of action has been identified in animal models. It is the Division's opinion that a mechanism of action has not been ruled out and that there may be cross reactivity with other receptors and ligands that have not been identified. Zelnorm is a 5-HT_4 partial agonist with moderate affinity for the 5-HT_1 receptor. There is recent medical literature proposing a link between Zelnorm and the development of Raynaud's phenomenon. The article presents a case history of a 21-year-old female, with no prior history of Raynaud's who developed painful discoloration of the fingers after exposure to cold, two days after initiating tegaserod (12 mg/day). Symptoms disappeared completely after drug therapy was stopped. The patient was not on any concomitant medication during this period (Pharmacoepidemiology and Drug Safety 2002; 11: 231-294). Another article discusses the potential risk of Zelnorm-induced myocardial infarction. The article, titled "Tegaserod-induced myocardial infarction: case report and hypothesis," proposes that since tegaserod has moderate affinity for the 5-HT_1 receptor, it is plausible that tegaserod could cause coronary artery contraction and spasm similar to other 5-HT_1 receptor agonists, such as those used for treating migraine (Pharmacotherapy 2004 Apr; 24 (4):526-31). Although these two articles are not conclusive, they do support the Division's position that a mechanism of action explaining an association between Zelnorm and ischemic colitis has not been ruled out.

Appendix 1

Dear Health Care Professional Letter. See end of this briefing document.

Appendix 2

Zelnorm Package Insert (April 2004). See end of this briefing document.

Appendix 3

Case Summaries

	Type	Case #	Age	Sex	Investigation	Meets Diagnostic Criteria**	Reported Ischemic Event
Reported as Ischemic Colitis							
1	SR	PHEH2003US03631	43	F	Colonoscopy Pathology	**Probable**	Y
2	SR	PHEH2003US04046	26	F	Colonoscopy Pathology	**Probable**	Y
3	SR	PHEH2003US04219	75	M	Colonoscopy	**Probable**	Y
4	SR	PHEH2003US05690	58	F	Colonoscopy Pathology	**Probable**	Y
5	SR	PHEH2003US06406	51	F	Colonoscopy Pathology	**Probable**	Y
6	SR	PHEH2002US10075	54	F	Colonoscopy Pathology	**Probable**	Y
7	SR	PHEH2003US02735	65	F	Colonoscopy Pathology	**Probable**	Y
8	SR	PHEH2003US06376	42	F	Colonoscopy Pathology	**Probable**	Y
9	SR	PHEH2003US06128	82	F	Colonoscopy Pathology	**Probable**	Y
10	SR	PHEH2003US11704	44	F	Colonoscopy Pathology	**Probable**	Y
11	SR	PHEH2004US00568	62	F	Colonoscopy Pathology	**Probable**	Y
12	SR	PHEH2004US00669	28	F	Colonoscopy Pathology	**Probable**	Y
13	SR*	PHEH2003US10301	76	F	Colonoscopy Pathology	**Probable**	Y
14	SR	PHEH2004US00854	30	F	Flex Sig Pathology	**Probable**	Y
15	SR	PHEH2004US01849	51	F	Colonoscopy	**Probable**	Y
16	SR	PHEH2003US09111	72	F	Colonoscopy	**Probable**	Y
17	SR	PHEH2003US09775	58	F	Colonoscopy	**Probable**	Y
18	SR	PHEH2004US02476	80	F	Sigmoid	**Not Adjudicated**	Y
19	SR	PHEH2004US02475	49	F	Sigmoid	**Not Adjudicated**	Y
20	SR	PHEH2003US07828	?	F	Unknown	**Undetermined**	Y
Reported as Intestinal Ischemia							
21	SR	PHEH2004US1080	61	F	Surgery	**Probable**	N
22	SR*	PHEH2004US1170	41	F	Surgery	**Probable**	Y
23	SR*	PHEH2003US10302	66	F	Surgery	**Probable**	Y

	Type	Case #	Age	Sex	Investigation	Meets Diagnostic Criteria**	Reported Ischemic Event
24	SR*	PHEH2003US07859	67	F	US X-ray	**Probable**	Y
Received between April 15, 2004 and June 1, 2004 (Includes Cases of Ischemic Colitis and Intestinal Ischemia)							
25	SR	PHBS2004CA04080		F	Colonoscopy	**Not Adjudicated**	Y
26	SR	PHEH2004US04856	52	F	Unknown	**Not Adjudicated**	Y
27	SR	PHEH2004US04754	33	F	Unknown	**Not Adjudicated**	N
28	SR	PHEH2004US04839	39	F	Unknown	**Not Adjudicated**	Y
29	SR	PHEH2004US04798	?	F	Unknown	**Not Adjudicated**	Y
20	SR	PHEH2004US05181	50	F	CT/Surgery	**Not Adjudicated**	Y
31	SR	CTU 219159	52	F	Colonoscopy	**Not Adjudicated**	Y
32	SR	PHEH2004US05151	78	F	Colonoscopy	**Not Adjudicated**	Y
33	SR	PHEH2004US05077	40	F	Unknown	**Not Adjudicated**	Y

* Deaths; **Meets diagnostic criteria for ischemic colitis or intestinal ischemia.

Case 1
PHEH2003US03631
6mg QD
Zelnorm start date: 12/17/02

Division's Review of the Case: Probable

43 y/o female, treated with Zelnorm since 12/17/02 for c-IBS, developed rectal bleeding abdominal pain on 04/17/03. The patient was admitted to the hospital -------- after symptoms of bloody diarrhea, abdominal pain, nausea, and vomiting progressed. A colonoscopy with biopsy was performed. The endoscopy report described ischemic colitis involving the splenic flexure to descending colon. The pathology report describes "features are more supportive of an ischemic process rather than inflammatory bowel disease." Stool cultures were performed, but the specimen and results were lost. The patient was discharged from the hospital --------.

The patient is reported to have had an episode of rectal bleeding (no mention of abdominal pain) a couple months prior to initiating Zelnorm. A colonoscopy was performed and was reported as normal.

Three weeks prior to this event, the patient was treated with Augmentin for a sinus infection.

The patient had a past medical history of c-IBS, hypertension, hyperlipidemia, rectocele repair, sinus surgery.

Outpatient medication:

Zestoretic	Zyrtec
Oral Birth Control	Zocor

Conclusion:

The available data suggest this represents a case of ischemic colitis. Both the colonoscopy and the biopsy support the diagnosis of ischemic colitis. It is unlikely to be an antibiotic induced infectious colitis since the classic finding of pseudo-membranes were not identified during the endoscopy and the process resolved without treatment for infectious colitis. The patient was also receiving oral hormone therapy, which could have contributed to developing ischemic colitis.

Case 2
PHEH2003US04046
6mg BID
Zelnorm start date: 1/28/03

Division's Review of the Case: Probable

26 y/o female, treated with Zelnorm since 1/28/03 for c-IBS, developed abdominal pain and bloody diarrhea on 05/06/03. The patient was evaluated by a gastroenterologist as an outpatient and a colonoscopy with biopsy was performed ----------. The endoscopy report describes superficial necrosis of the proximal descending colon with "classic appearance of ischemic colitis." The pathology report describes "features compatible with ischemic colitis." Stool cultures were not obtained.

Outpatient medication:

Yasmin **(**Oral Birth Control)
Excedrin

Conclusion:

The available data suggest represents a case of ischemic colitis. Both the colonoscopy and the biopsy support the diagnosis of ischemic colitis. The patient was also receiving oral hormone therapy, which could have contributed to developing ischemic colitis.

Case 3
PHEH2003US04219
6mg BID
Zelnorm start date: Unknown

Division's Review of the Case: Probable

75 y/o male, treated with Zelnorm for c-IBS, was admitted to the hospital -------- with abdominal pain and hematochezia. On --------, a colonoscopy was performed which demonstrated "changes suspected for ischemic colitis" involving the transverse colon.

The patient had a baseline colonoscopy -------- that demonstrated diverticulosis, and a colon polyp.

The AERS report describes the patient had a past medical history of chronic abdominal pain, suspected ischemic bowel disease, diverticulosis, colon polyp, arthrosclerosis, TIA,

Outpatient medication:

Pamelor	Prednisone	Tenormin	Imdur	Altace
Protonix				
K-Dur	Pravachol	Lasix	Norvasc	Aspirin
Azmacort				
Albuterol	Theo-Dur	Flovent	Combivent	Nitroglycerin

Conclusion:

Although the available data are limited, it suggests this represents a case of ischemic colitis. The patient had a vague past medical history of ischemic colitis.

Case 4
PHEH2003US05690
6mg BID
Zelnorm start date: 6/18/03

Division's Review of the Case: Probable

58y/o female, treated with Zelnorm since 6/18/03 for IBS, developed abdominal pain, rectal bleeding, and hypotension and was admitted to the hospital on --------. A sigmoidoscopy with biopsy was performed -------- that demonstrated "ischemic colitis involving the sigmoid and descending colon" and a diminutive rectosigmoid polyp. The path report describes "features suggestive of ischemic colitis."

The patient had a past medical history of colon polyps, hemorrhoids, GERD, hiatal hernia, depression, hypertension, hypercholesterolemia, asthma, hypothyroidism,

fibromyalgia, gastritis, degenerative disk disease, anxiety, endometriosis, headache, tubal ligation, hysterectomy, cholecystectomy, bladder surgery, kidney stones.

Outpatient medication:

Trandolapril	hydrochlorothiazide	Nexium
Premarin	Advair Diskus	Folic Acid
Singulair	Estrace	Norflex
Rhinocort	Nasonex	Vitamin B12
Covera (verapamil)		

Conclusion:

The available data suggest this represents a case of ischemic colitis. The patient was also receiving oral hormone therapy, which could have contributed to developing ischemic colitis.

Case 5
PHEH2003US06406
2mg QID
Zelnorm start date: 5/20/03

Division's Review of the Case: Probable

51y/o female treated with 2mg Zelnorm QID since 5/20/03 for c-IBS, developed severe abdominal pain, diarrhea and rectal bleeding on --------. The patient was admitted to the hospital the following day. A colonoscopy with biopsy was performed -------- that demonstrated ischemic colitis involving the splenic flexure (40-55cm). The biopsy report from 50cm describes "chronic ischemic colitis." No stool cultures were performed.

The physician did not suspect Zelnorm was related to the ischemic colitis and restarted the patient on Zelnorm on 7/16/03.

The patient in a non-smoker with a past medical history of IBS, hypertension, peptic ulcer disease, chronic back pain, spinal stenosis, hysterectomy, back surgery.

Outpatient medication:

Ultracet	Fiorinal	Caltrate
Norvasc	Lisinopril	Pantoprazole
Bextra	Neurontin	Estradiol (Transdermal)

Conclusion:

The available data suggest this represents a case of ischemic colitis. The patient was also receiving oral hormone therapy, which could have contributed to developing ischemic

colitis. There is no additional information on whether the patient tolerated the re-challenge.

Case 6
PHEH2002US10075
6mg
Zelnorm start date: 11/7/02

Division's Review of the Case: Probable

54y/o female treated with 6mg Zelnorm since 11/7/02 for c-IBS developed abdominal bloating, explosive diarrhea and hypotension approximately 1-½ hours after taking the first dose of Zelnorm. The patient was evaluated in the ER and discharged. Later that evening ---------- the patient developed bloody diarrhea and returned the ER and was admitted. A colonoscopy with biopsy was performed -------- that demonstrated an ulcerated friable mucosa in the transverse colon. The biopsy report described superficial ulcerations of the epithelial cells, infiltrated by acute and chronic inflammatory cells with some dropout of the glands seen in the acute crypts. Stool cultures were reported as negative. The physician's impression was "friable area most likely secondary to transient ischemia of the bowel, most likely to dehydration."

A prior colonoscopy dated -------- described a polyp in the descending colon, small lesion in the sigmoid colon and a small arteriovenous malformation.

The patient has a past medical history of GERD, colon polyp, c-IBS, hypercholesterolemia, migraine, hysterectomy, and varicose vein stripping.

Outpatient medication:
Rabeprazole Ranitidine Citrucel

Conclusion:

The available data suggest this represents a case of ischemic colitis. Both the colonoscopy and biopsy support the diagnosis of ischemic colitis. It is unlikely that this episode of ischemic colitis, in a 54 y/o female, would be caused by dehydration.

Case 7
PHEH2003US02735
6mg BID
Zelnorm start date: 3/17/03

Division's Review of the Case: Probable

65 y/o female was initially worked up for abdominal pain on --------, prior to receiving Zelnorm. The patient had a CT scan of the abdomen and pelvis, which was significant for diverticulosis, no evidence of diverticulitis. The patient was started on 6mg Zelnorm BID on 3/17/03 for symptoms of constipation and abdominal pain. The patient presented to the ER on -------- with worsening abdominal pain, bloating, explosive diarrhea, and hypotension. The patient was evaluated in the ER. The ER physician suspected diverticulitis and treated the patient with Augmentin. The patient was discharged from the ER. Zelnorm was discontinued 3/20/03. A CT of the abdomen and pelvis performed -------- demonstrated a "suggestion of subtle thickening involving the distal transverse colon" with "haziness of the surrounding fat", "a change since the previous study --------."

The patient was evaluated with colonoscopy and biopsy on ---------, which demonstrated multiple diverticula in the recto-sigmoid and descending colon. The mucosa of the splenic flexure was reported as ulcerated, white, thickened, and irregular with a differential diagnosis "rule out ischemic colitis. The biopsy is described as "mild focal active colitis (colonic tissue with focal crypt injury by neutrophils).

A follow up colonoscopy, performed --------, reported no evidence of inflammation or ulceration.

The patient has a past medical history of hyperparathyroidism, breast cancer, hysterectomy, cholecystectomy, questionable history of diverticulitis (ER visit), GERD, COPD.

Outpatient medication:

Milk of Magnesia	Augmentin (ER visit)
Advil	Theophylline
Aciphex	BuSpar

Conclusion:

The available data suggest this represents a case of ischemic colitis. However, the patient did have abdominal pain prior to receiving Zelnorm, with no suspicious findings on CT dated --------. The patient's symptoms changed and worsened after initiating Zelnorm therapy. Both the colonoscopy and biopsy support the diagnosis of ischemic colitis. A follow up colonoscopy, performed --------, demonstrated resolution of inflammatory/ulcerating processes.

Case 8
PHEH2003US06376
12mg BID (patient error)
Zelnorm start date: 9/16/02

Division's Review of the Case: Probable

42 y/o female developed acute onset severe abdominal pain, diarrhea and rectal bleeding after one days therapy of 12mg Zelnorm BID (9/17/02). The patient was prescribed 6mg BID, but inadvertently took 12mg BID. The patient was evaluated by sigmoidoscopy on --------, which demonstrated "changes consistent with ischemic colitis."

The patient was a non-smoker with a past medical history of hypertension.

Outpatient medication:

Diovan	Enulose
Citrucel	Milk of Magnesia

Conclusion:

> The available data suggest this represents a case of ischemic colitis that occurred after an accidental overdose, twice normal. Symptoms occurred after one day of therapy, in a patient with no known risk factors for ischemic colitis.

Case 9
PHEH2003US06128
6mg BID
Zelnorm start date: 10/25/02

Division's Review of the Case: Probable

82 y/o female, treated with Zelnorm since October 25, 2002 for c-IBS, developed bloody diarrhea on November 14, 2002. A colonoscopy with biopsy was performed on --------. The gastroenterologists' impression was "colitis, left sided. Suspect ischemic vs. infection. Less likely inflammatory bowel disease." The pathology report states, "mild nonspecific active colitis with increased eosinophils and features focally suggestive of ischemic colitis."

The patient was discharged home on Cipro and Flagyl.

The patient had a past medical history of diverticulosis, colonic polyps, non-specific colitis, chronic ulcerative colitis, and "one bout of ischemic colitis", type II diabetes, hypertension, and decreased memory.

MedWatch report updated August 13, 2003:

> The "Gastroenterologist confirmed the final diagnosis to be infectious colitis, not ischemic colitis"

MedWatch report updated August 19, 2003:

The pathologist states “she did not call it ischemic”; therefore she was not convinced it was ischemic colitis. Furthermore, she states she used “focally suggestive of ischemic colitis to cover all the bases.”

Conclusion:

The available data suggest this represents a case of ischemic colitis. However, the patient’s past medical history includes non-specific colitis, chronic ulcerative colitis, and “one bout of ischemic colitis.”

The Gastroenterologists’ follow-up statement was made after the fact, although he had not seen the patient in follow-up. Additionally, there is no mention of the results of a culture report to support this case being infectious colitis.

The initial pathology report describes findings suggestive of ischemic colitis. The explanation that she was not convinced it was ischemic colitis and only used the phrase “focally suggestive of ischemic colitis to cover all the bases” is unacceptable. The pathologist only described the left colon as focally suggestive of ischemic colitis, the same area the Gastroenterologist described as possible ischemic colitis.

Case 10

PHEH2003US11704
6mg BID
Zelnorm start date: 11/13/02

Division’s Review of the Case: Probable

44 y/o female, treated with Zelnorm since 11/13/02 for c-IBS, developed severe left lower quadrant abdominal pain with bloody diarrhea on 12/13/03. The patient was evaluated in the emergency room. The work-up included a CT scan of the abdomen, which demonstrated fat stranding in the pericolonic region. Stool cultures were reported negative. The patient was not admitted to the hospital. She was discharged on Cipro.

On --------, a sigmoidoscopy with biopsy was performed that demonstrated “moderately active colitis, suspect ischemic colitis.” Ulcerations were reported in the splenic flexure. Biopsies of the splenic flexure revealed focal active colitis and ulceration with accompanying acute and chronic inflammation with granulation tissue formation. Features “consistent with active colitis and suspicious for ischemic colitis”.

The patient had a past medical history of gastroparesis, c-IBS, chronic constipation, depression, and migraines. The report states the patient was worked up in the distant past for Crohn’s Disease, but was never diagnosed with it. A baseline colonoscopy performed in 2002 was described as normal.

Outpatient medication:

Citalopram	clonazepam
Macrogol	lansoprazole

Conclusion:

The available data suggest this represents a case of ischemic colitis.

Case 11
PHEH2004US00568
6mg
Zelnorm start date: 12/17/03 (one day)

Division's Review of the Case: Probable

62 y/o female, treated with Zelnorm on 12/17/03 for constipation, developed nausea and vomiting, abdominal pain and diarrhea on 12/17/03. The patient was evaluated in the emergency room at --------. The patient continued to be symptomatic. By ----------, the patient had several episodes of bright red blood per-rectum without fecal material. The patient had a leukocytosis of 13.7k.

The patient was treated with I.V. fluids and I.V. antibiotics (levofloxacin and metronidazole).
On --------- a colonoscopy with biopsy was performed that demonstrated ulcerated, erythematous, edematous mucosa from 25-40cm from the anal verge, with no evidence of diverticulitis. The gastroenterologists' impression was "colitis, localized, that may represent ischemic colitis." The pathology report describes severe active colitis with erosions and pseudomembrane formation with a histologic differential of ischemic injury or of C- Difficile. Stool cultures were reported negative. The patient was discharged on ---------- with a diagnosis of ischemic colitis.

The patient had a past medical history of hemorrhoids, constipation, migraines, osteoporosis, hysterectomy, hip surgery and pneumonia treated with antibiotics ---------.

Outpatient medications:

Premarin	ASA

Conclusion:

The available data suggest this represents a case of ischemic colitis. The patient was also receiving oral hormone therapy, which could have contributed to developing ischemic colitis. It is unlikely that this represented C-difficile colitis. The patient had negative stool cultures and she had no recent risk factors for developing C-difficile colitis.

Case 12

PHEH2004US00669
6mg QD
Zelnorm start date: 8/7/2003 – 10/15/2003

Division's Review of the Case: Probable

28 y/o female, treated with Zelnorm since 8/7/2003 for c-IBS, developed vomiting, abdominal pain and bloody diarrhea on 10/14/03. The patient was admitted to the hospital on -------- with a leukocytosis of 13.1k. A CT scan ---------, was reported as unremarkable.

On --------, the patient had a sigmoidoscopy with biopsy that demonstrated a 10cm segment of ulcerated, edematous mucosa between 40-50cm from the anal verge. Biopsies were reported as "acute and chronic colitis with cryptitis and in one section crypt attenuation suggesting ischemic colitis." Stool cultures were negative. The patient was treated with I.V. hydration, levofloxacin, and metronidazole.

The patient was discharged from the hospital on --------. The patient had a follow-up colonoscopy performed --------- that was described as normal mucosa.

The patient had a past medical history of constipation and IBS, tendonitis, mild depression.

Outpatient medications:

Drospirenone ethinylestradiol
Valdecoxib Escitalopram (selective serotonin reuptake inhibitor (SSRI))

Conclusion:

The available data suggest this represents a case of ischemic colitis. The patient was also receiving oral hormone therapy, which could have contributed to developing ischemic colitis. However, drospirenone ethinylestradiol was continued after discharge from the hospital.

Case 13
PHEH2003US10301
6mg BID
Zelnorm start date: 11/18/2002 – 08/02/2003

Division's Review of the Case: Probable

76 y/o female, treated with Zelnorm since 11/18/02 for c-IBS, developed nausea, and severe abdominal pain on 8/26/03. The patient was found on the floor by her family. The patient was evaluated in the emergency room and was hypotensive, dehydrated,

hypothermic, with rigors and complaining of nausea and severe abdominal pain. She was in her usual state of health the day before this episode.

The work-up included a CT scan of the abdomen, which demonstrated a thickened proximal descending colon with pericolonic inflammatory changes in the left colon. On admission, blood chemistries revealed WBC (18.7k), amylase (322), and lipase (53). She had a nasogastric tube placed to suction and was treated with I.V. hydration, and parenteral levofloxacin and metronidazole.

On --------, the patient had a *MR angiogram* to evaluate positive guaiac stools; no evidence of mesenteric occlusion was identified. A surgical consult was obtained. The Surgeon's impression was diverticulitis vs. ischemic colitis. A colonoscopy with biopsy was performed ---------, which demonstrated "*ischemic changes between 25-60cm*" from the anal verge. The sigmoid and splenic flexure were reported to have "deep penetrating ulcerations, some of which had dark mucosa suggesting small areas of necrotic bowel." The pathology report describes findings as "*most consistent with the clinical history of ischemic colitis.*" Additionally, there were areas of exudative changes reported as possibly diverticulitis.

The patient was placed on total parenteral nutrition (TPN) via central line. A follow-up colonoscopy 2-3 weeks later described resolving ischemic colitis.

The patient was discharged on -------- to a long-term facility. A follow-up colonoscopy was performed ---------. This was limited to 55cm due to a poor prep, but the visualized segment was described as improved colonic mucosa.

On --------, the patient was noted to be lethargic, hypotensive and febrile. The patient was diagnosed with an E. coli urinary tract infection. A repeat CT of the abdomen demonstrated persistent left colon inflammation. On --------, the patient was re-admitted to the hospital because of possible sepsis, pyrexia and weakness. The patient developed line sepsis and grew staphylococcus and enterococcus species from the central line tip. Blood cultures were positive for enterococcus and candida.

Due to her advanced age and comorbidities the family made her Do Not Resuscitate (DNR) on --------. Her antibiotics were discontinued on ---------. The patient expired ----------

The patient had a past medical history of constipation, IBS, sigmoid diverticulosis, colon abscess, spinal stenosis with laminectomy, urinary retention secondary to neuropathy, Alzheimer's disease, bilateral mastectomy for breast cancer 1991, cholecystectomy 1981.

Outpatient Medications:

Neurontin	Celexa	Fosamax	Elavil
MiraLax	Xanax	Ruminal	Celebrex

Conclusion:

The available data suggest this represents a case of ischemic colitis. Although the Sponsor attributes the patient's death to sepsis from central line, the Medwatch report lists "cause of death was sepsis related to ischemic bowel disease." This patient only required a central line to treat the complications of ischemic colitis. Therefore, if the use of Zelnorm resulted in this patient developing ischemic colitis, this patient's death was contributed to by the use of Zelnorm. Additionally, as the use of Zelnorm increases in the elderly and nursing home population, similar cases as this with withdrawing or limiting medical/surgical interventions will occur.

Case 14
PHEH2004US00854
6mg bid
Zelnorm start date: 3/03 - 6/30/03

Division's Review of the Case: Probable

30 y/o female, treated with Zelnorm since 11/18/02 for c-IBS. On 6/29/03, the patient was evaluated for a 4-day history of bright red blood per rectum and bloody diarrhea. The patient had a sigmoidoscopy with biopsy performed on --------, which demonstrated a 20cm segment of colitis involving the rectum. The pathology report of the rectum describes areas of sclerosis with atrophic, shrunken, distorted glands and dilated vessels, suggestive of chronic ischemic colitis. Zelnorm was discontinued. On ---------, the patient had a follow-up sigmoidoscopy with biopsy that was reported as normal.

The physician reported that he felt the ischemic colitis was related to Zelnorm use, based on the diagnosis of ischemia in a young woman "still taking estrogen," with "normal mucosa before and after (discontinuing) Zelnorm."

The patient had a past medical history significant for only IBS.

Outpatient Medication:
Estrogen

Conclusion:

The available data suggest this represents a case of ischemic colitis. The patient was also receiving oral hormone therapy, which may have contributed to developing ischemic colitis. However, the patient was continued on estrogen and has not had a recurrence of ischemic colitis to date.

Case 15
PHEH2004US01849
6mg bid

Zelnorm start date: 1/19/2004- 2/5/04

Division's Review of the Case: Probable

51-y/o female, treated with Zelnorm since 1/19/04 for IBS, developed abdominal pain and bloody diarrhea. On 2/5/04 the patient woke from sleep at 2am with severe abdominal pain and diarrhea. Shortly after this, she developed bloody diarrhea. The patient presented to the ER -------- with 10/10 abdominal pain and a leukocytosis of 16k. The ER physician's impression was ischemic colitis.

The bloody diarrhea persisted for 2 days and slowly resolved, while in the hospital. Stool cultures were negative. A colonoscopy with biopsy was performed --------, which demonstrated colitis affecting the descending colon, splenic flexure and transverse colon, with minimal diverticulosis. The endoscopist's impression was mild colitis, "suspect ischemic colitis, healing". The Pathology report describes changes consistent with early changes of ischemic colitis.

Patient was discharged from the hospital ---------.

The patient related no prior history of similar episodes and reported that for three days prior to this event, she experienced intense abdominal cramping after each dose of Zelnorm.

The patient is a non-smoker with a past medical history of IBS, chronic abdominal pain, cholecystectomy, hypertension, and appendectomy.

Outpatient Medications:

Aceon	Hormone patch
Zelnorm	Actonel

Conclusion:

The available data suggest this represents a case of ischemic colitis. The patient was also receiving transdermal hormone therapy, which may have contributed to developing ischemic colitis. However, the patient was continued on transdermal hormone therapy and has not had a recurrence of ischemic colitis to date.

Case 16
PHEH2003US09111

Zelnorm 6mg QD

Zelnorm start date: 8/31/03 – 9/5/03

Division's Review of the Case: Probable

The patient is a 72 y/o female with a complicated history of recurrent incisional hernias. The patient was admitted to the hospital three times in the two weeks prior to the admission in question.

During a work up for the incisional hernia, a CT scan of the abdomen demonstrated a large incarcerated ventral hernia with approximately half of her bowel in the subcutaneous space with no evidence of strangulation. The patient was admitted to the hospital -------- for repair of recurrent hernia. The surgery was described as difficult secondary to extensive adhesions. During dissection, a 4cm serosal injury to the colon occurred. Additionally, due to loss of domain, attempts to primarily close the hernia defect resulted in pulmonary compromise. The facial defect was ultimately closed with two pieces of mesh, a 10x6 inch piece of Gore-Tex and a 8x14 inch piece of Prolene mesh.

On an unspecified date after surgery, the patient developed sepsis and hypotension requiring dopamine and Levophed. On 8/31/03, the patient was started on Zelnorm to treat a postoperative ileus. Zelnorm was discontinued after 6 days (9/5/03) when the patient "became more septic."

On --------, the patient had a repeat CT scan of the abdomen that demonstrated post-surgical changes with questionable abdominal wall cellulitis vs. abscess. On --------, the patient had another CT and a colonoscopy was performed to evaluate abdominal distention, absent bowel sounds, and decreasing oxygenation. The CT described diffuse gaseous distention of the colon, possible ileus, possible pulmonary aspiration, and a right pleural effusion. The colonoscopy described copious amounts of liquid stool with ischemic appearing mucosa. A decompressing rectal tube was placed. No biopsies were obtained.

The physician reported the patient had completely recovered.

The patient had a past medical history of coronary artery disease, COPD, obesity, ventral hernia repair.

Conclusion:

The patient had signs and symptoms of sepsis requiring vasopressor support before receiving Zelnorm. The patient status deteriorated prior to receiving Zelnorm and continued to deteriorate after Zelnorm was initiated.

Case 17
PHEH2003US09775
6mg BID
Zelnorm start date: 10/13/03

Division's Review of the Case: Probably

58 y/o female, treated with Zelnorm since 10/13/03, developed abdominal pain and bright red blood per rectum. Patient presented to the hospital for an urgent colonoscopy with biopsy that same day. The colonoscopy demonstrated hemorrhagic, edematous mucosa of the rectum, and a few small-scattered diverticula in sigmoid and descending colon and a diminutive polyp in the transverse colon. The differential included "R/O ischemic colitis." The pathology report describes fragments of the rectal mucosa showing mild, nonspecific chronic inflammation. The patient was also reported to have moderate non-bleeding hemorrhoids.

The Patient had a follow-up colonoscopy -------- that described the mucosa in the terminal ilium as erythematous (Biopsy Normal), a 5mm sessile polyp in ascending colon, 22mm polyp in the transverse colon, diverticula in sigmoid colon, and large internal non-bleeding hemorrhoids. The impression for this colonoscopy was rectal bleeding most likely due to internal hemorrhoids.

The patient had a past medical history of hypertension, colonic polyp, and hysterectomy.

Conclusion:

The report from the colonoscopy performed -------- suggests possible ischemic colitis. The Division requested and reviewed the color photographs from the procedure. The photos were not representative of the descriptive terms used in the report and only demonstrated a single small punctate area. Understanding the limitations of endoscopic photos, the patients presentation and endoscopic report support the possibility of ischemic colitis.

Case 18
PHEH2004US02476

Zelnorm 6mg QD
Zelnorm start date: 12/10/2003

Division's Review of the Case: Not Adjudicated

80 y/o female with a history of c-IBS was treated with Zelnorm since 12/10/2003. The patient was instructed to take 6mg Zelnorm QD with instructions to increase to BID as needed. On --------- the patient was admitted to the hospital with sudden onset left sided abdominal pain, nausea, and passing bright red blood with clots per rectum. A CT scan on ---------- reported a long segment of bowel wall thickening involving the descending colon with some pericolonic inflammatory changes. The CT report described findings questionable for diverticulitis versus ischemic bowel. A sigmoidoscopy with biopsy to the mid-descending colon was performed on ----------, which demonstrated diverticula in

the sigmoid colon (no mention of descending colon diverticula) with punctate erythema in the mid-descending colon. Biopsies were reported as ischemic colitis.

Patient slowly improved on antibiotics and was discharged ----------.

The patient had a past medical history of a diverticulosis, colon polyp, questionable history of abdominal adhesions, hypertension, hyponatremia, anxiety, laminectomy

Social history is significant for cigaret smoking.

Outpatient medications:

Vistaril	Betimol (opth)
Lortab	Refresh (opth)
Diovan	

Conclusion:

The available data suggest this represents a case of ischemic colitis. The CT scan was suspicious for ischemic colitis. Both the sigmoidoscopy and the biopsies support the diagnosis of ischemic colitis. It is unlikely that this episode was diverticulitis based on the location of the diverticula (sigmoid colon) and the location of the inflammatory changes (descending colon)

Case 19
PHEH2004US02475

Zelnorm 6mg QD
Zelnorm start date: 11/20/2002

Division's Review of the Case: Not Adjudicated

49 y/o female with a history of IBS was treated with Zelnorm since 11/20/2002. On ----------, the patient was admitted to the hospital for a right thoracoscopy with lung biopsy. The patient was discharged on -------- with the diagnosis of interstitial pulmonary fibrosis and treated with a steroid taper dose. The patient was re-admitted to the hospital on ------- with chest pain. A chest x-ray demonstrated a 50% pneumothorax and a chest tube was placed. Over the following 24 hours, the patient developed progressive mid-epigastric and left lower quadrant abdominal pain. On --------, an emergency laparotomy was performed. The patient was reported to have ischemic colon with necrosis and near perforation of the descending and sigmoid colon. The surgeon expressed concern that the ischemic event was related to Zelnorm use. The patient underwent a left hemicolectomy and sigmoidectomy with colostomy. The patients status improved and she was discharged form the hospital on --------.

The patient had a past medical history of CHF, Oxygen, and CPAP dependent COPD, sleep apnea, hypertension, GERD, actinic keratosis, dyslipidemia, osteoarthritis, rheumatoid arthritis, trauma induced DVT, obesity, cholecystectomy, tendon surgery

Outpatient medications:

Diovan	Lasix	Percocet	Zoloft	Wellbutrin
Astelin	Ultram	Bextra	Flexeril	Soma
Compazine	Proventil	Singulair	Pulmicort	Flonase
Duoneb	Prednisone	Colace	Tiazac	Prevacid
Levsin	Azithromycin			

Conclusion:

The available data suggest this represents a case of intestinal ischemia. The patient's complex past medical history does not explain her development of ischemic bowel.

Case 20
PHEH2003US07828
Dose: Unknown
Zelnorm start date: Unknown

Division's Review of the Case: Undetermined

A mother reported to her physician that her daughter developed ischemic colitis while taking Zelnorm. The mother refused to allow any information to be released.

Conclusion:

Insufficient information available. The Division will contact the physician who reported this case and will ask his/her assistance with obtaining additional information.

Case 21
PHEH2004US1080

Zelnorm 6mg
Zelnorm start date: 9/1/03

Division's Review of the Case: Probable

61 y/o female, treated with Zelnorm since 9/1/03 for c-IBS. On --------, the patient was evaluated in the ER for a 1-week history of progressive nausea and vomiting, and constipation. As part of her work-up, an abdominal x-ray was performed, which identified air in the wall of the small bowel and portal vein. The patient had an

emergency exploratory laparotomy performed and was found to have marked small bowel and colonic dilatation. The proximal small bowel was described as ischemic. The surgical report states the bowel became pinker and appeared viable when it was delivered from the abdomen. Lysis of adhesions was performed, however a point of obstruction was not identified. The ileum, liver stomach, duodenum, and left colon were normal. The final diagnosis was abdominal compartment syndrome with pneumatosis intestinalis of unknown ideology.

Postoperatively, the patient required prolong ventilatory support and required a tracheostomy --------. On --------, a CT scan of the abdomen described nonspecific wall thickening of the rectum and sigmoid colon, consider infectious, or inflammatory colitis, "ischemic colitis is considered less likely." The patient also developed a central line infection. Following removal of this line, the patient had a PIC line placed.

The patient had a past medical history of Type I diabetes mellitus, gastroparesis, tardive dyskinesia, hysterectomy, salpingectomy, appendectomy, breast cancer, hypothyroidism secondary to radioactive ablation of hyperthyroid, IBS, chronic constipation.

Outpatient medications:

Insulin	Synthroid	Tamoxifen	Zelnorm
Actonel	Aspirin	Procrit	Iron sulfate
B12	Seroquel		

Conclusion:

The patient developed abdominal compartment syndrome with pneumatosis intestinalis. There was no evidence of a segmental colitis or findings suggestive of ischemic colitis. The ischemic description of the small bowel resolved after the compartment syndrome was relieved.

Case 22
PHEH2004US1170

Zelnorm 6mg BID
Zelnorm start date: Unknown

Division's Review of the Case: Probable

41 y/o female, treated with Zelnorm for an unknown duration to treat c-IBS, developed severe abdominal pain on 1/19/04. On the morning of ---------, the patient woke up, stood, and collapsed with loss of consciousness. Emergency personnel were called and administered cardio-pulmonary resuscitation. The patient was treated with vasopressors. While in the ER, a plain x-ray identified a large amount of free air in the abdomen. The patient had an emergency exploratory laparotomy performed and was found to have a

gangrenous left colon with full thickness necrosis from the splenic flexure to descending colon. The remaining colon appeared ischemic to the terminal ileum. A fecal impaction was also described. The patient underwent a colectomy with ileostomy. Postoperatively, the patient remained hypotensive in spite of vasopressors Dopamine and Levophed and required continued ventilator support. The patient was removed from life support on ---------- and died.

The patient had a past medical history of a ruptured appendix requiring limited colon resection, IBS, chronic constipation, GERD, hiatal hernia, asthma, COPD, obsessive compulsive disorder, bipolar disorder, lumbar surgery, hypothyroidism, hysterectomy, cervical cancer, recurrent bladder infection, and peripheral vascular disease, claudication with non-palpable pedal pulses.

Social history is significant for 1½ - 3 packs of cigarettes/day, history of illicit drug and alcohol abuse use approximately 10 years prior to event.

Outpatient medications:

Seroquel Ambien Albuterol Levoxyl
Lithobid (on/off, none for past year)

Conclusion:

The available data suggest this represents a mesenteric artery occlusion. The MedWatch report describes the patient had a history of non-compliance, a 90 pack-year history of cigarette use and peripheral vascular disease. The treating physician stated that the patients did not have a diagnostic workup for peripheral vascular disease. The diagnosis of claudication was based on her history and physical. The patient related pain in her legs while walking but denied rest pain.
The treating physician described the patient as having non-palpable pedal pulses, with no physical evidence of advanced peripheral vascular disease (no ulcers, wounds, or dermatitis). The patient had no history of vascular surgeries and did not describe signs or symptoms of intestinal angina.

Case 23
PHEH2003US10302

Zelnorm 6mg QD
Zelnorm start date: 10/10/03 (Question if patient ever received Zelnorm)

Division's Review of the Case: Probable

The patient was a 66 y/o female with a complicated history of postprandial abdominal pain and weight loss since 1/00. The patient developed pain in the lower abdomen, occurring approximately 30 minutes after eating. The patient weighed 128 pounds in

March 2000. By October 2002, the patient's symptoms were associated with chronic diarrhea, which was treated with Lomotil.

In November 2002, the patient was re-evaluated for persistent postprandial abdominal pain and diarrhea and a 10-pound weight loss. She was noted to be heme positive. A colonoscopy performed -------- identified a non-specific colitis. The patient was started on Asacol for the colitis and Vicodin for pain.

The patient's symptoms continued and she was evaluated by two gastroenterologists. In September 2003, the patient had a CT scan and a sigmoidoscopy that were reported as normal. The patient's weight was recorded at 92 pounds. On 10/10/03, the patient was given samples and a prescription for Zelnorm. The patient's weight was recorded at 88 pounds.

On ---------, the patient was admitted to the hospital with severe bloody diarrhea and abdominal pain. She was initially treated with intravenous fluids and morphine. Plain x-rays of the abdomen described calcifications of the iliac and splenic arteries. A CT scan of the chest, dated ---------, described scattered vascular calcification in the thoracic aorta and markedly dense calcifications in the left subclavian. On --------, the patient developed an acute abdomen and was evaluated by a vascular surgeon. The Surgeon's impression was "probable chronic intestinal ischemia, acutely worse." The patient had an emergency exploratory laparotomy and was found to have ischemic changes of the entire small bowel, cecum, and ascending colon. Findings consistent with occlusion of the superior mesenteric artery. The patient expired on ---------. The cause of death is reported as "bowel infarction due to peripheral vascular disease."

The patient had a past medical history of hypertension, COPD related to cigaret smoking, rheumatoid arthritis, and a four-year history of IBS with abdominal pain, alternating diarrhea, and constipation.

Conclusion:

The patient had signs and symptoms of advanced peripheral vascular disease and intestinal angina that progressed over the past 4 years. In additional to postprandial abdominal pain, diarrhea, and weight loss, the patient was also noted to be heme positive with a non-specific colitis, prior to receiving Zelnorm. Furthermore, the patient's husband, who was the primary caregiver, does not recall giving her Zelnorm.

Case 24

PHEH2003US07859

Zelnorm 6mg BID
Zelnorm start date: 6/16/03

Division's Review of the Case: Not Adjudicated

67 y/o female with a history of IBS initiated Zelnorm on 6/16/2003. On --------, the patient was admitted to the hospital with progressive chest pain radiating down her right arm, shortness of breath and pain in her lower extremities. The admitting diagnosis was rule out myocardial infarction. The differential diagnosis also included rhabdomyolysis, possibly from use of Lipitor. On admission, her abdomen was described as soft, non-tender and obese. There was no report of diarrhea, bright red blood per rectum or melena. An EKG demonstrated atrial fibrillation with a controlled ventricle response. Laboratory studies demonstrated a WBC: 7.9, increased CPK: 403 (MB:21), troponin <0.5, increased K: 6.4, decreased Na: 126, increased BUN/Cret: 75/1.9.

A renal ultrasound on -------- was reported as negative. On -------, the patient complained of abdominal pain. A surgical consult was obtained, which described a soft, non-distended abdomen, with left lower quadrant pain, possible diverticulitis. A plain abdominal x-ray on that day described a large amount of stool in the colon with no gaseous distention or free air. The patient progressed to respiratory failure and was intubated. The patient was hypotensive, requiring "pressors." Laboratory studies on ----------demonstrated an amylase/lipase of 7,570/424. A pulmonary and cardiology consult was obtained. The differential diagnosis included pneumonia, rule out abdominal sepsis, rule out ischemic colitis, coronary heart disease and hypotension. The patient did not respond to therapy. On ---------, the patient was made "no code" and died. A discharge summary note describes "surgery examined the patient and they felt that the patient likely has ischemic bowel syndrome."

The patient's past medical history was described by her family doctor and included: coronary heart disease with bypass surgery, diabetes, hypertension, cholecystectomy with associated pancreatitis --------, GI bleed with diarrhea ---------, angioplasty with stent, congestive heart failure, obesity, hyperlipidemia, mitral valve disorder, atrial fibrillation, peripheral neuropathy, urinary incontinence and infection, chronic and acute renal failure.

Outpatient medications:

Potassium	Aldactone	Plavix	Urecholine
Meclizine	Aspirin	Protonix	Xanax
Insulin	Warfarin	Digoxin	Amiodarone
Zaroxolyn	Lasix	Cardizem	Imdur
Altace	Lipitor		

Conclusion:

The patient had a very complex past medical history as well as hospitalization. In addition to the patients underlying medical conditions, the patient had a history of a GI bleed with diarrhea on --------, before the start date of Zelnorm (6/16/03).

It appears the patient did not have abdominal complaints at time of admission. The initial admitting diagnosis was rule out MI. Additionally, the patient was identified as possibly having rhabdomyolysis at time of admission with a CPK of 403. On --------, the patient

developed abdominal pain and respiratory failure. A surgical consult, two days after admission, described a soft abdomen with left lower quadrant pain, possible diverticulitis. At that time, the patient was also reported to have elevated pancreatic enzymes. This episode could represent bowel ischemia. A typical presentation for ischemic bowel includes abdominal pain out of proportion to physical exam (soft abdomen) and the increased amylase/lipase could be consistent with bowel ischemia.

Case 25

PHBS2004CA04080

Zelnorm ?
Zelnorm start date: ?

Division's Review of the Case: Not Adjudicated

"Classical picture of IC in a young female patient treated with recommended doses of Zelmac for 1 to 2 weeks."

Conclusion:

Very limited information was available at this time. However, the report does state the treating physician describes the findings classic for ischemic colitis.

Case 26

PHEH2004US04856

Zelnorm: 6mg BID
Zelnorm start date: April 12, 2004

Division's Review of the Case: Not Adjudicated

52 y/o female with a history of IBS, initiated Zelnorm on 4/12/2004. The patient developed rectal bleeding on 4/27/04. A colonoscopy was performed on --------- that demonstrated friable mucosa of the descending colon "very typical of ischemic colitis."

The patient's past medical history included: "redundant sigmoid"

Outpatient medications: not reported

Social history: not reported

Conclusion:

The available data suggest the patient developed ischemic colitis approximately 2 weeks after starting Zelnorm therapy. The colonoscopy with biopsy supports the diagnosis of ischemic colitis.

Case 27

PHEH2004US04754

Zelnorm: unknown
Zelnorm start date: October 2003

Division's Review of the Case: Not Adjudicated

Very limited information was available at this time. A 33y/o female developed bloody diarrhea, fever, and chills approximately 6 months after initiating Zelnorm for an unspecified indication.
The patient was hospitalized on -------- with the diagnosis of colitis. Zelnorm was discontinued. The patient was treated with antibiotics and discharged on ---------.

Conclusion:

Very limited information was available. However, the report does state the treating physician describes the findings suspicious for ischemic colitis. The Sponsor has requested additional information.

Case 28

PHEH2004US04839
6mg BID
Zelnorm start date: July 1, 2003

Division's Review of the Case: Not Adjudicated

39 y/o female, marathon runner, developed abdominal pain, bloody diarrhea and fever on 4/19/2004, approximately 9 months after initiating Zelnorm therapy. The patient completed a 26-mile marathon just prior to becoming symptomatic.

The patient had a CT scan of the abdomen and pelvis, which was significant for thickening of the wall of the cecum and ascending colon with a small amount of hemorrhage into the cecal wall. GI and surgical consults were obtained. The treating diagnosis was "non-occlusive ischemic colitis." The patient did not have a work up for a hypercoagulable condition.

The patient was treated with antibiotics and bowel rest and improved. The patient was discharged form the hospital --------.

Conclusion:

The available data suggest this represents a case of ischemic colitis. The treating physician reported the ischemic colitis might have been caused by the patient's recent marathon race, "a rare complication of marathon running," and that "Zelnorm may have made this more likely."

Case 29

PHEH2004US04798

6mg QD
Zelnorm start date: unknown

Division's Review of the Case: Not Adjudicated

Very limited information was available at this time. A female patient (age not specified) was hospitalized with the diagnosis of ischemic colitis, 2-3 days after taking 6mg tegaserod. The report states the diagnosis of ischemic colitis was confirmed by colon biopsy. No other information was provided. The report states the "physician reported event is not related to Zelnorm."

Conclusion:

The report states the treating physician describes the findings suspicious for ischemic colitis. It is unclear what other risk factors the patient had for developing ischemic colitis. The Sponsor has requested additional information.

Case 30

PHEH2004US05181

Zelnorm: Unknown Dose
Zelnorm start date: August 17, 2003

Division's Review of the Case: Not Adjudicated

50 y/o female with a history of constipation and colon polyps initiated Zelnorm on 8/17/2003 for constipation. The patient had a long history of severe constipation unresponsive to laxatives and required frequent manual disimpaction. On --------, the patient was admitted to the hospital with severe abdominal pain, nausea, and vomiting. There was no evidence of fecal impaction on rectal exam. A CT scan demonstrated

thickening of the duodenum and proximal jejunum with portal venous gas and bowel wall pneumatosis. The patient had a leukocytosis of 33.6k and elevated amylase/lipase (380/2109).

The clinical impression included acute pancreatitis, ischemic bowel, small bowel obstruction, and vascular pathology. The patient had a "second-look" surgery (date unspecified) and was found to have small bowel ischemia. A segmental resection of the small bowel was performed. The patient is reported to have slowly recovered.

The patient's past medical history included severe constipation, chronic abdominal pain, CVA, migraines, Nissen fundoplication, appendectomy, hysterectomy, colon polyp, pancreatitis, peptic ulcer.

Outpatient medications: not reported

Social history includes cigarette use (unspecified) and alcoholism.

Conclusion:

The patient developed small bowel ischemia five days after initiating Zelnorm therapy. It is uncertain whether the patient had one or two surgeries. The report describes a "second look" surgery. The surgeon is reported as not knowing what caused the ischemic process. This suggests the process was not related to adhesions. It is unlikely that the ischemia was caused by pancreatitis.

Case 31

2mg BID
Zelnorm start date: April 2, 2004

Division's Review of the Case: Not Adjudicated

52 y/o female initiated Zelnorm on 4/2/2004 for irritable bowel syndrome and constipation. The patient developed abdominal pain nausea, vomiting, bloody diarrhea, and hypotension (86/36) and was hospitalized --------. The patient received one dose of Zelnorm while in the hospital and had continued bloody mucus stool. A colonoscopy with biopsy was performed that demonstrated findings consistent with ischemic colitis in the descending colon. The patient was discharged from the hospital on --------.

The patient's past medical history included: irritable bowel syndrome and constipation.

Outpatient medications: Aciphex, Oxazepam

Social history: not reported

Conclusion:

The report included very limited information. However, it does suggest the patient developed ischemic colitis of the descending colon approximately 4 weeks after initiating Zelnorm therapy. During this event, the patient was also hypotensive (86/36). It is unclear whether the hypotension was the result of the ischemic event or the cause of the ischemic event.

Case 32

PHEH2004US05151

3mg BID
Zelnorm start date: March 18, 2004

Division's Review of the Case: Not Adjudicated

78 y/o female with a prior history of sigmoid resection for diverticular disease (unknown date) initiated Zelnorm on 3/18/2004 for bloating. The patients presenting symptoms were not reported. However, on ---------, the patient had a colonoscopy with biopsy that was reported as "ischemic colitis like findings." Zelnorm was discontinued on May 5, 2004.

The patient's past medical history included: hypertension, fundoplication, cholecystectomy, and sigmoidectomy.

Outpatient medications: not reported

Social history: not reported

Conclusion:

Very limited information was available at this time. The report does suggest the patient developed bowel ischemia approximately 5 to 6 weeks after starting Zelnorm therapy. The Sponsor has requested additional information.

Case 33

PHEH2004US05077

6mg BID
Zelnorm start date: April 27, 2004

Division's Review of the Case: Not Adjudicated

40 y/o female with a history of cerebral palsy (confined to wheelchair) initiated Zelnorm on 4/27/2004 for c-IBS. The patient developed rectal bleeding and was hospitalized on ------, with the diagnosis of ischemic colitis. Zelnorm was discontinued on May 4, 2004.

The patient's past medical history included: hypertension, fundoplication, cholecystectomy, and sigmoidectomy.

Outpatient medications: not reported

Social history: not reported

Conclusion:

Very limited information was available at this time. However, the report does state the patient developed ischemic colitis approximately 1 week after starting Zelnorm therapy. The Sponsor has requested additional information.

DRAFT

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-200 (SE1-005)
Drug Name:	Zelnorm (tegaserod maleate) Tablets
Indication(s):	Approved: Short-term treatment of women with irritable bowel syndrome (IBS) whose primary bowel symptom is constipation. Proposed in this supplement: Treatment of patients with chronic constipation and relief of associated symptoms of straining, hard or lumpy stools and infrequent defecation
Applicant:	Novartis Pharmaceutical Corporation
Date(s):	Submitted October 20, 2003
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 2 (HFD-715)
Statistical Reviewer:	Joy Mele, M.S.
Concurring Reviewers:	Stella Grosser, Ph.D. Team Leader
Medical Division:	Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Clinical Reviewers:	Robert Prizont, M.D. (HFD-180) (Efficacy) Gary Della'Zanna, M.D. (HFD-180) (Safety)
Project Manager:	Paul Levine, Jr., R.Ph., J.D. (HFD-180)

Keywords: Clinical studies, rescue medications, repeated measures

1. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

Zelnorm (tegaserod) is an aminoguanidine indole compound which through the "activation of 5-HT_4 agonists triggers the release of neurotransmitters from the enteric nerves resulting in increased contractility and stimulation of the peristaltic reflex" (page 8 of the protocol for Study 2301). Zelnorm is presently approved for the treatment of constipation-IBS in women.

1.1 Conclusions and Recommendations

The applicant has presented the results of two clinical trials; 2301, predominantly a European study and 2302, predominantly an USA study. Most of the patients were female (88%), under 65 years old (87%) and Caucasian (~90%) and had a long history of constipation (median of 12 years). About 60% of the patients had a history of laxative use and about 53% used laxatives during the 2-week baseline period. At screening, the main constipation complaints reported by about half the patients were abdominal distension/bloating or infrequent defecation. Less than 5% of the patients entered the trial with a diagnosis of IBS, although about ? of the patients exhibited IBS-like symptoms. Patients had fewer than 3 complete spontaneous bowel movements per week during the baseline period.

The table below summarizes the results for the primary efficacy variable (responder defined as a patient having a mean increase of ≥ 1 CSBM/week for the first 4 weeks of the study) and for the FDA medical division's preferred efficacy variable (responder defined as a patient having a mean of ≥ 3 CSBM/week). Results for the first month showed statistically significant treatment effects for both doses of Zelnorm versus placebo with a dose response relationship evident for Study 2301 but not for Study 2302. Analyses for Months 2 and 3 showed significant treatment effects for Zelnorm 6 mg versus placebo in both studies but no significant results for Zelnorm 2 mg in Study 2301.

Table 1.1 Percentage of patients responding for the first month (primary endpoint) and percentage of patients responding for all three months

	Study 2301			**Study 2302**		
	PLA n=416	ZEL 2 n=417	ZEL 6 n=431	PLA n=447	ZEL 2 n=450	ZEL 6 n=451
Weeks 1-4						
Inc≥1 CSBM/wk	28% (112/406)	**36%** (146/403)	**42%** (176/420)	26% (113/431)	**42%** (185/436)	**45%** (197/439)
≥3 CSBM/wk	13% (53/409)	**19%** (79/409)	**23%** (96/423)	14% (60/433)	**23%** (102/440)	**24%** (104/441)
Respond all 3 months All pts						
Inc≥1 CSBM/wk	15% (60/411)	**20%** (83/409)	**24%** (102/423)	15% (64/434)	**24%** (107/441)	**26%** (113/442)
≥3 CSBM/wk	8% (31/411)	10% (39/409)	**12%** (52/423)	7% (31/434)	**14%** (61/441)	**12%** (61/441)

About 43% of the Zelnorm 6 mg patients have an average increase of 1 or more CSBM during the first month compared to about 27% of the placebo patients (Table 1.1); about half of these patients in each group are responders for all 3 months of the study. Only about 10% more of the Zelnorm 6 mg patients than placebo patients respond with a mean increase of 1 or more CSBM for all 3 months. The difference between Zelnorm 6 mg and placebo is only 5% when looking at an average of 3 or more CSBM per week. So looking at the responder data by month shows statistically significant effects for Zelnorm 6 mg over placebo but also shows that less than 1/5 of the patients reap a benefit above placebo.

Analyses of the average daily change in CSBM for the full 12 weeks (Table 3.10) and the number of weeks responding (Table 3.12), both showed significant treatment effects for the 6 mg dose.

Analyses of the following subgroups revealed treatment effects (Zelnorm-placebo) consistent with the overall effects:

- baseline laxative users and non-users
- non-users of laxatives during the entire trial
- non-IBS-like patients (applicant's analysis)
- by baseline CSBM and baseline SBM
- by years of constipation
- by main constipation complaint except those patients complaining of abdominal pain

Notable inconsistencies in subgroups are the following:

- The interaction of treatment by gender was borderline significant at p=0.11. Males showed a smaller nonsignificant treatment effect (about 6-9% on both responder variables) compared to a treatment effect of about 10-17% for females (Table 4.2) with the largest difference seen for the primary efficacy variable.
- The interaction of treatment by age was significant at p=0.04. The treatment effect for older patients was generally less than half the effect seen for younger patients.
- Patients with a main constipation complaint of abdominal pain (about 12% of the patients) had a treatment effect for the 6 mg dose about one-third the effect seen for the overall population (Table 4.5).

Overall comments:

- A dose response was seen in Study 2301 but not in Study 2302 for reasons for discontinuation (Tables 3.2 and 3.3) and for efficacy (tables 3.9 and 3.10 and Figure 3.1).
- Analyses of both change in CSBM and total number of CSBM consistently showed, regardless of statistical method or variable definition (e.g. by month, by week, observed, etc.), statistically significant treatment effects for Zelnorm 6 mg BID over placebo.
- The mean treatment effect for the 6 mg dose over placebo is an increase of less than 1 CSBM/week. About 42% of the Zelnorm 6 mg patients and 26% of placebo patients had an increase of 1 or more CSBM/week during the first month of treatment.
- About 40% of Zelnorm patients did <u>not</u> experience 3 or more CSBM at any week on

trial. Zelnorm 6 mg patients who completed the trial had 3 or more CSBM for a median of 2 to 3 weeks out of 12 weeks (Table 3.12) compared to about 1 week for placebo.

- Laxative used was high at baseline (about 53%) with most patients continuing to take laxatives on study (Table 3.6). There was a small decline in laxative use in the 6 mg dose group with the odds of using laxatives decreasing significantly compared to placebo ($p<.03$). Also the number of weeks of laxative use was statistically significantly less for the 6 mg group than for the placebo group though the numerical mean difference was very small (<1 week). The distributions for the groups is shown in Appendix 7. So a decline in laxative use is seen but may be clinically insignificant.
- Since inconsistent results are seen for males and most of the patients studied were females, it seems that the results for females cannot be readily generalized to males.
- Only 13% of the patients were 65 or older; older patients showed a significantly smaller treatment effect than younger patients. So Zelnorm has shown minimal efficacy in a subgroup that may comprise a large part of the target population.
- Withdrawal of Zelnorm in Study 2302 resulted in a significant drop in CSBM's and responders (Figure 3.2).
- Only about 37% of the patients randomized to Zelnorm in Study 2301 were able to complete the 13-month extension study. Efficacy data was not adequate to determine maintenance of the Zelnorm effect.

1.2 Brief Overview of Clinical Studies

The applicant's two clinical trials (Studies 2301 and 2302, Table 1.2) were conducted under essentially the same protocol. The trials differed in how patients who completed the 12 weeks of double-blind phase were treated at the end of treatment. For Study 2301, patients could continue in to a blinded extension phase where patients on Zelnorm continued on their same dose and placebo patients were switched to Zelnorm 6 mg. For Study 2302, drug was withdrawn from all patients and patients were followed for an additional 4 weeks.

Table 1.2 Clinical Trials

Study Location and # of centers Dates conducted	Design	Treatment groups (N)	Duration
E2301 Europe South Africa Australia 7/01 to 6/02	Randomized, double-blind, placebo-controlled, parallel	Zelnorm 2 mg BID (417) Zelnorm 6 mg BID (431) Placebo (416)	2 Weeks Baseline 12 Weeks Trt
E2301E1 extension study 10/01 to 3/21/03	double-blind, uncontrolled, parallel	Zelnorm 2 mg BID (284) Zelnorm 6 mg BID (283) Pla/Zel 6 mg BID (275)	13 Months Trt
E2302 USA Canada South America 6/01 to 4/02	Randomized, double-blind, placebo-controlled, parallel	Zelnorm 2 mg BID (450) Zelnorm 6 mg BID (451) Placebo (447)	2 Weeks Baseline 12 Weeks Trt 4 Weeks Withdrawal Follow-up

1.3 Statistical Issues

There were two major issues in Studies 2301 and 2302. The first issue was the selection of patients for the trials. The medical reviewer, Dr. Prizont, was concerned that the population studied was not representative of patients with functional/idiopathic constipation, "the most common form of constipation" (Dr. Prizont's review). Prevalence of functional/idiopathic constipation is highest among the elderly and equally likely in males and females; however, both the elderly (~13%) and men (~12%) were under-represented in both studies. In addition, the medical reviewer was concerned that patients in these studies were not screened for IBS (Zelnorm is already approved for constipation-IBS). To address the question of whether the results may be generalized to patients with characteristics of functional/idiopathic constipation, this reviewer performed analyses of subgroups defined by age, gender, baseline bowel movements and presenting constipation complaint. Also included in the review are analyses performed by the applicant of subgroups defined by entry criteria and IBS-like symptoms.

The second major issue of concern was the definition of the primary endpoint. These concerns were both clinical and statistical. The primary endpoint was a responder endpoint where responders were defined as patients with a mean decrease of one or more CSBM per week averaged over the first 4 weeks of the trial. The clinical concern expressed by the medical reviewer, Dr. Prizont, was that patients could remain constipated by definition (fewer than 3 CSBM/week) but yet be considered responders. This latter concern was addressed in two ways in this review; 1) analysis of a protocol-specified secondary variable where responders are patients with 3 or more CSBM per week and 2) subgroup analyses based on baseline CSBM to determine if patients with no CSBM or only 1 CSBM show benefit from Zelnorm treatment.

Additional statistical concerns regarding the primary endpoint which are addressed in the review include the following:

- use of imputed data by the applicant versus observed data
- choice of week as the unit of measurement
    - the analysis of the first 4 weeks as the primary outcome

Other statistical issues included the observation of a large placebo response and the impact of rescue medication on efficacy; the latter was of particular concern since laxative use was high and patients remained on study regardless of laxative use.

2. Introduction

2.1 Overview

Zelnorm (tegaserod) is an aminoguanidine indole compound which through the "activation of 5-HT_4 agonists triggers the release of neurotransmitters from the enteric nerves resulting in increased contractility and stimulation of the peristaltic reflex" (page 8 of the protocol for Study 2301). Zelnorm is presently approved for the treatment of constipation-IBS in women.

The applicant has submitted the results of two clinical trials (Studies E2301 and E2302, henceforth referred to as 2301 and 2302, Table 2.1) to support the efficacy and safety of Zelnorm for the treatment of chronic constipation characterized by infrequent defecation, straining, bloating and hard stools. Both trials were conducted under essentially the same protocol. Patients completing Study 2301 could be treated in Study E2301E1, a 13-month extension study while patients completing Study 2302 had treatment withdrawn and were followed for 4 weeks.

Table 2.1 Clinical Trials

Study Location and # of centers Dates conducted	Design	Treatment groups (N)	Duration
E2301 Europe South Africa Australia 7/01 to 6/02	Randomized, double-blind, placebo-controlled, parallel	Zelnorm 2 mg BID (417) Zelnorm 6 mg BID (431) Placebo (416)	2 Weeks Baseline 12 Weeks Trt
E2301E1 extension study 10/01 to 3/21/03	double-blind, uncontrolled, parallel	Zelnorm 2 mg BID (284) Zelnorm 6 mg BID (283) Pla/Zel 6 mg BID (275)	13 Months Trt
E2302 USA Canada South America 6/01 to 4/02	Randomized, double-blind, placebo-controlled, parallel	Zelnorm 2 mg BID (450) Zelnorm 6 mg BID (451) Placebo (447)	2 Weeks Baseline 12 Weeks Trt 4 Weeks Withdrawal Follow-up

2.2 Data Sources

The NDA was submitted only electronically and is stored at the following address in the CDER's Electronic Document Room: \\Cdsesub1\n21200\S_005\2003-10-20.

The applicant also provided the reviewer with a well-organized and sufficiently described database consisting of both raw data directly from the case report forms and derived data.

All tables and figures presented in this review were created by the reviewer unless otherwise noted.

3. Statistical Evaluation

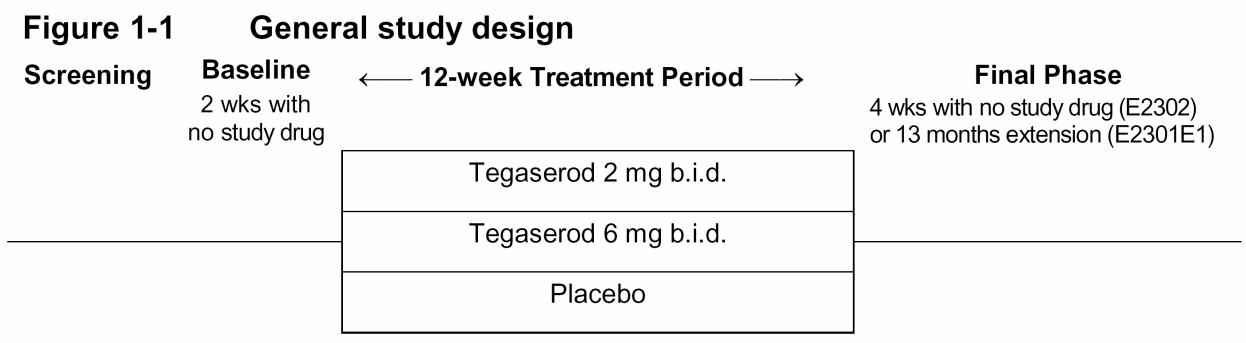
3.1 Evaluation of Efficacy

3.1.1 Studies 2301 and 2302

Design

Studies 2301 and 2302 were randomized, double-blind trials with patients randomized to Zelnorm 2 mg BID, Zelnorm 6 mg BID or placebo. Medication was to be taken 30 minutes before breakfast and 30 minutes before the evening meal. The treatment periods are illustrated in the applicant's schematic below. Patient visits were scheduled at Week –2, Day 1 (randomization) and Weeks 4, 8, and 12. Patients were asked to record in both daily and weekly diaries (see Appendix 1 for details) and to complete a dietary survey regarding fiber in his/her diet. In Study 2301, patients could enter a 13 month extension study (E2301E1) while in Study 2302 patients remained on study without study medication for 4 weeks of withdrawal.

Figure 3.1 Applicant's schematic of the trial design for Studies 2301 and 2302 (from Section 2.5 of the NDA)



The primary endpoint in both trials was the number of complete spontaneous bowel movements (CSBM). Complete refers to a feeling of complete evacuation as reported in the diary and spontaneous refers to no laxative use 24 hours before a BM. A responder analysis was the primary analysis with a responder defined as a patient, who was on study for at least 7 days during the first 4 weeks of the study, with a mean increase of 1 or more in CSBM per week compared to baseline over the first 4 weeks of the study. All other patients were considered non-responders. Baseline was computed based on the number of days of data during the 2-week baseline period just prior to randomization.

Secondary endpoints included the following:

- the number of CSBM and responders during 12 weeks of treatment
- bowel habit (frequency, form, straining, feeling of complete evacuation)

- patient's assessment of bowel habits, constipation, distension/bloating and abdominal discomfort/pain
- laxative use
- safety and tolerability

Quality of life (QOL) measured by the SF-36 and the EQ-5D was studied as a tertiary endpoint. Also ß-carotene was measured at screening and endpoint to assess the effect on vitamin absorption.

Enrollment criteria included (but were not limited to) the following:
- males and females 18 or older
- 6-month history and diary confirmation during baseline (average of 2 weeks of baseline) of constipation which was defined as follows:
    - <3 CSBM per week and one or more of the following characteristics observed with spontaneous BM's:
        - at least 25% of stools are hard or very hard
        - incomplete evacuation with at least 25% of BM
        - straining with at least 25% of BM

    OR
    - all BM's preceded by laxative use

- no history of laxative abuse
- no history of medical conditions thought to cause constipation

Rescue medication (laxative bisacodyl, 5-15 mg per day) was allowed if a patient had not had a BM for at least 4 days (96 hours). Use of concomitant medications that affect bowel habits was not permitted. Study medication could be discontinued for up to 48 hours due to diarrhea.

Pharmacogenomic evaluations were planned to find genetic markers for diagnostic purposes and to identify patients with maximal response or those more susceptible to adverse events. The applicant's report states that these results will be "reported separately" and are considered exploratory research. At the time of this review, no pharmacogenomic evaluations have been performed according to the applicant.

Patient Disposition

In Study 2301, a total of 1,633 patients were screened in centers in Europe, Australia and South Africa; 1,264 patients (77%) were randomized (Table 3.1) at 128 centers in 18 countries. Germany and The Netherlands enrolled the most patients with about 12% of the patients from each country. In Study 2302, a total of 1,954 patients were screened in centers in North and South America; 1,348 patients (83%) were randomized (Table 3.1) at 105 centers in 7 countries. About 80% of the randomized patients in Study 2302 were enrolled in the United States.

The trial was powered at 90% to detect a 12% treatment effect for each pairwise comparison (assuming a 30% responder rate for placebo and a 42% rate for Zelnorm) with 395 patients per group. The applicant actually enrolled 416 to 451 patients in each treatment group.

More than 90% of the patients completed the first 4 weeks in all treatment groups of both studies and more than 80% completed the double-blind part of the trial (Table 3.1). Across the study, only about 1% of the patients still on study were missing bowel movement (BM) data for a particular week (see the bottom section of Table 3.1).

The disposition data shows sufficient retention of patients and no notable problem with missing data suggesting that dropouts or missingness did not impact the interpretation of the statistical results.

Table 3.1 Studies 2301 and 2302 Patient Disposition

	Study 2301			**Study 2302**		
	PLA	ZEL 2	ZEL 6	PLA	ZEL 2	ZEL 6
Randomized	416 (100%)	417 (100%)	431 (100%)	447 (100%)	450 (100%)	451 (100%)
Wk 4	93%	95%	92%	93%	96%	93%
Wk 8	86%	87%	88%	86%	90%	86%
Complete DB (Wk 12)	342 (82%)	347 (83%)	359 (83%)	361 (81%)	380 (84%)	375 (83%)
Pts w/ BM data by week						
Wk 1	409	408	423	433	438	440
Wk 2	401	399	415	425	431	430
Wk 3	398	395	404	421	429	422
Wk 4	387	391	397	413	423	416
Wk 5	375	385	389	402	416	408
Wk 6	362	367	379	385	401	397
Wk 7	358	363	377	381	399	395
Wk 8	355	360	378	379	400	393
Wk 9	351	354	370	372	393	385
Wk 10	341	349	360	359	385	379
Wk 11	337	347	355	357	385	374
Wk 12	337	343	350	353	377	369
WD 1				358	382	373
WD 2				341	368	360
WD 3				336	365	353
WD 4				313	334	327

The reasons for discontinuing treatment during the double-blind phase of the trials are summarized in Table 3.2 on the following page. The groups are comparable with regard to dropouts due to patient request, protocol violation and

lost-to-follow-up. In the European study, 2301, about twice as many patients (8%) in the Zelnorm 6 mg group drop due to an adverse event (most commonly abdominal pain) than in the other two groups (4-5%). In Study 2302, essentially an US study, the ADE rates are comparable across the groups, but the lack-of-efficacy dropout rates differ. About twice as many placebo patients (9%) drop due LOE than in the other two groups (4-5%).

Table 3.2 Studies 2301 and 2302 Reasons for discontinuation

	Study 2301			**Study 2302**		
	PLA n=416	ZEL 2 n=417	ZEL 6 n=431	PLA n=447	ZEL 2 n=450	ZEL 6 n=451
ADE	5%	4%	8%	2.5%	3%	3%
LOE	5%	4%	3%	9%	5%	4%
Pt req	3%	3%	3.5%	3%	4%	5%
Prot. Viol.	2%	1%	1%	2%	1%	1%
Lost-to-FU	2%	4%	2%	2.5%	2%	3%
Other	<1%	<1%	<1%	<1%	<1%	<1%

This reviewer examined the ADE data (Post-text listings 10-3) more carefully and summarized the ADE reasons in Table 3.3. It is very clear that significantly more patients drop out in the high dose group (Zelnorm 6 mg) for a GI ADE compared to the other two groups. There appears to be an association between treatments and ADE's. This is consistent with both the applicant and the clinical reviewer of safety (Dr. Gary Della'Zanna) reports of dose-related incidences of diarrhea.

Table 3.3 Studies 2301 and 2302 Number of patients by ADE reason

	Study 2301			**Study 2302**		
	PLA n=416	ZEL 2 n=417	ZEL 6 n=431	PLA n=447	ZEL 2 n=450	ZEL 6 n=451
GI reason	12	9	22	5	10	12
Pregnancy	1	0	0	3	1	1
Other	8	6	11	3	3	2

Baseline Demographics

The patient population in both studies was predominantly female (about 86%, Table 3.4 on the following page) with only a total of 173 males in Study 2301 and 135 males in Study 2302. The average age was about 47 years, with about 14% of the patients in Study 2301 and 12% of the patients in Study 2302, 65 years or older. The majority of the patients were Caucasian. According to entry criteria, patients needed to have experienced constipation for the 6 months prior to randomization; the majority of patients reported more than 3 years of constipation. Median duration of constipation was about 5 years longer in Study 2302 than 2301 (Table 3.4).

Table 3.4 Studies 2301 and 2302 Baseline Demographics for All Randomized Patients

	Study 2301			Study 2302		
	PLA n=416	ZEL 2 n=417	ZEL 6 n=431	PLA n=447	ZEL 2 n=450	ZEL 6 n=451
Age						
Mean (SD)	46 (16)	47 (16)	46 (15)	47 (14)	47 (15)	47 (13)
Range	18-85	18-86	18-85	18-84	20-88	18-84
%=65years	14%	16%	11%	13%	13%	9%
%=75years	4%	4%	4%	2%	5%	3%
Gender						
% Female	87%	86%	86%	91%	89%	90%
Post-Meno (% of F)	39%	44%	46%	45%	45%	46%
Race						
% Caucasian	98%	98%	98%	84%	85%	85%
% Black	<1%	<1%	<1%	7%	8%	7%
Duration of constipation (yrs)						
Mean (SD)	14.5 (13)	14.1 (12)	15.5 (15)	20.2 (16)	19 (15)	19.3 (15)
Median	10	10	10	16	15	15
Range	0.5-70	0.5-71	0.5-67	0.5-66	0.5-70	0.5-60
Prior Disease						
GERD	19%	16%	17%	18%	19%	19%
Biliary Colic	4%	3%	4%	2%	2%	2%
Non-ulcer dyspepsia	11%	12%	11%	4%	4%	4%
IBS	2%	2%	4%	3%	4%	5%
Acq.Hypothyroidism	3%	3%	3%	11%	8%	7%
Prior Trt						
Laxatives/enema	58%	58%	57%	66%	63%	63%
Diet	40%	40%	39%	51%	54%	53%
Natural remedies	26%	28%	25%	26%	25%	26%
Bulking agents	25%	25%	27%	44%	42%	40%
Exercise	26%	21%	21%	43%	44%	43%
Main Complaint previous 6 months						
Abd. distension/bloat.	32%	29%	30%	24%	27%	26%
Infrequent defecation	16%	17%	16%	24%	26%	27%
Abdominal pain	14%	15%	17%	10%	10%	8%
Incompl. evacuation	15%	14%	11%	16%	13%	16%
Straining	11%	12%	14%	14%	13%	11%
Hard stools	11%	13%	11%	10%	10%	12%
Other	1%	<1%	1%	1%	<1%	<1%

Less than 5% of the patients entered the trials with a diagnosis of IBS; according to the medical reviewer, this is a group that should have been excluded from the trial since the indication is for chronic constipation not associated with IBS (constipation-type IBS is an approved Zelnorm indication).

The main gastrointestinal complaint based on the six months prior to randomization was abdominal distension and bloating; the second most frequent complaint was infrequent defecation.

The baseline values for the efficacy variables are summarized in Table 3.5 on the following page. Baseline values for bowel movements were computed from 14 days of diary data. Missing days were imputed from the average of the days with recorded data so number of bowel movements was not necessarily a whole number. About 77% of the patients in each study had 14 days of baseline data;

another 14% had 13 days of data; so the means for bowel movements are not appreciably affected by the imputation scheme.

The mean number of total bowel movements during baseline was about 4/week in 2301 and about 4.7/week in 2302; so patients had on average about 8-9 spontaneous and non-spontaneous bowel movements during the two week baseline period. On average, patients had only 1 CSBM during the 2-week baseline; more than half of the patients had no baseline CSBM (Table 3.5). The distributions for baseline CSBM and SBM are shown in Appendix 2.

Table 3.5 Studies 2301 and 2302 Baseline for efficacy variables

	Study 2301			**Study 2302**		
	PLA n=416	ZEL 2 n=417	ZEL 6 n=431	PLA n=447	ZEL 2 n=450	ZEL 6 n=451
BM per week						
Mean (SD)	4.1 (3.0)	3.9 (2.5)	4.0 (2.7)	4.7 (3.1)	4.6 (3.2)	4.7 (3.2)
Median	3.0	3.2	3.2	3.8	4.0	4.0
% 0	0.2%	0.2%	0.2%	0.5%	0.2%	0.2%
CSBM per week						
Mean (SD)	0.49 (0.78)	0.54 (0.84)	0.53 (0.92)	0.59 (0.87)	0.55 (0.79)	0.58 (0.82)
Median	0	0	0	0	0	0
(% pts)						
0	59%	52%	56%	50%	51%	52%
>0 to <1	15%	21%	20%	19%	20%	19%
1 to <2	18%	18%	13%	22%	19%	19%
2 to <3	7%	7%	8%	7%	6%	9%
≥3	2%	2%	3%	2%	3%	2%
SBM per week						
Mean (SD)	3.2 (3.1)	3.1 (2.7)	3.0 (2.9)	3.7 (3.3)	3.6 (3.3)	3.5 (3.4)
Median	2.2	2.5	2.5	3.0	2.7	2.5
(% of pts)						
0	11%	10%	11%	8%	6%	12%
>0 to <1	10%	9%	8%	7%	7%	5%
1 to <2	19%	17%	17%	15%	20%	18%
2 to <3	17%	16%	20%	16%	16%	15%
3 to <4	12%	18%	14%	17%	14%	14%
≥4	32%	30%	31%	38%	37%	37%
SBM reported at screening						
Mean (SD)	1.3 (1.1)	1.5 (1.4)	1.4 (1.1)	1.5 (3.9)[1]	1.4 (1.5)	1.4 (1.3)
Median	1	1	1	1	1	1
Stool consistency Mean[1]	2.5	2.5	2.3	2.6	2.8	2.9
Median Scores[2]						
Satisfaction w/bowels	3.0	3.0	3.0	3.0	3.0	3.0
Bothersomeness of						
Constipation	3.0	3.0	3.0	3.0	3.0	3.0
Bloating	3.0	2.5	2.5	3.0	3.0	3.0
Pain	2.0	2.0	2.0	2.0	2.0	2.0

1 Stool consistency is measured on a 7-point scale with lower numbers indicating harder stools. See Appendix 1 for a full description of the scores.

2 The scale used for the scores ranged from 0 ("a very great deal satisfied" for bowel habits and "not at all bothersome" for the other three) to 4 ("not at all satisfied" for bowel habits and "a very great deal bothersome" for the other three. See Appendix 1 for a full description of the scores.

1- The large standard deviation is due to one patient reporting an average of 80 SBM/week over the previous 6 months. This patient only had 4 SBM during the 14-day baseline.

About 45% of the patients in Study 2301 (the foreign study) and about 53% of the patients in Study 2302 (the predominantly US study) had 3 or more spontaneous bowel movements at baseline. So about half the patients had fewer than 3 spontaneous bowel movements per week during the baseline period. From discussions with Dr. Prizont (the FDA medical reviewer) and a cursory look at the literature, this reviewer understands that constipation is often defined by two or fewer spontaneous bowel movements a week. About half the patients in these trials do not meet the latter criterion.

Interestingly, 89% of the patients reported at screening less than 3 SBM per week on average for the previous 6 months; while during baseline only about half the patients report less than 3 SBM per week. About ¾ of the patients reported a higher number of SBM at baseline than at screening. So it appears that reporting in diaries during the initial 2 weeks (even without blinded medication) resulted in a higher reporting of bowel movements; this may contribute to the high placebo responder rate seen in the studies.

Treatment and diary compliance

Pill counts were only collected by the investigator at the individual sites; the pill count data was not recorded in the database nor analyzed by the applicant. So no information on drug compliance is available.

Looking at the diary data by week, this reviewer found that at each week more than 90% of the patients still on study recorded data for all 7 days; about 5-7% had diary data for 6 days. The "lowest" compliance occurred during the first and last week of the study (Weeks 1 and 12); again though the percentage of patients with <u>any</u> missing diary data was small (<13%). The average number of days patients recorded data over the full 12 weeks was 6.8 days per week<u>. About half of the patients recorded data for all 7 days for every week they were on study</u>; in addition, more than 20% of the patients were missing only 1 diary entry during their total time on trial. These results are seen across the treatment groups and across the studies. So diary compliance was high whether one examined the data by week or by patient. The latter is important because of the procedure used to calculate CSBM; missing CSBM data was imputed as the mean of the days on which data was observed, inflating the total number of CSBM for that week. This reviewer checked the impact of missing data on the change in CSBM and found that the results for patients with complete data were more favorable to the drug, in general, than the results for patients with incomplete data (albeit a small number of patients); so it appears that the inflation of the CSBM number by imputation did not bias the treatment comparison in favor of the drug. Nevertheless, since the treatment effects are small, this reviewer did additional analyses to further examine the impact of imputation on the results; these analyses and results are described in the efficacy section of this review.

Laxative Use

About 53% of the patients in each treatment group had a history of using laxatives before enrollment in the trial. Laxative use (bisacodyl, 5-15 mg per day) was allowed during baseline and double blind treatment if a patient went four days without a bowel movement. About half of patients (53% in Study 2301 and 51% in Study 2302) used laxatives during the baseline period (Table 3.6). Most patients with baseline use of laxatives used laxatives at some time while on study; so regardless of treatment, patients who were in the habit of using laxatives continued to use laxatives at least once during the study. About 15% of 2301 patients and about 20% of 2302 patients did not use laxatives at baseline but did on study with the highest percentage seen for placebo (Table 3.6). About a third of the patients in each study used no laxatives.

Table 3.6 Studies 2301 and 2302 Any laxative use during baseline and DB periods

	Study 2301			**Study 2302**		
Laxative use	PLA n=416	ZEL 2 n=417	ZEL 6 n=431	PLA n=447	ZEL 2 n=450	ZEL 6 n=451
Baseline only	11%	13%	15%	9%	12%	14%
Baseline+DB	42%	40%	39%	40%	39%	40%
DB only	17%	16%	12%	21%	17%	13%
No base/No DB	30%	31%	34%	30%	32%	34%

Table 3.7 shows the distribution of baseline SBM by baseline laxative use. As would be expected, the distributions are quite different with most patients not using laxatives having more than 2 baseline SBM's and most patients using laxatives having 2 or fewer SBM's. The median number of SBM's in patients with baseline laxative use is 2 SBM's while in patients without baseline laxative use, the median is about 4 SBM's. So adjusting in an analysis for either baseline spontaneous BM's or baseline laxative use is essentially the same adjustment.

Table 3.7 Studies 2301 and 2302 Baseline SBM by baseline laxative use

	Study 2301						Study 2302					
	PLA		ZEL 2		ZEL 6		PLA		ZEL 2		ZEL 6	
Baseline laxative use	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
N	219	193	221	189	231	197	219	223	231	213	239	210
Baseline SBM												
0	19%	0.5%	18%	0%	19%	1%	16%	1%	12%	0.5%	23%	0.5%
1-2	55%	18%	52%	17%	52%	17%	45%	11%	53%	16%	42%	17%
>2	26%	82%	30%	83%	29%	82%	38%	88%	35%	84%	35%	83%

Patients taking laxatives are less likely to have spontaneous bowel movements (in fact, patients with zero SBM's at baseline were all on laxatives); clearly this

follows from the fact that a lack of a spontaneous BM for four days can lead to the taking of a laxative. So the use of laxatives by habit may subjugate the effectiveness of the drug. Yet, about one third of the patients took no laxatives at baseline or on treatment so they provide a subgroup in which to assess the effect of Zelnorm without the confounding of laxative use.

Laxative use by study week is shown in Appendix 3. At every week in both trials (with the exception of Week 3 in Study 2302), laxative use was highest in the placebo group compared to the high dose group by about 8-10% in Study 2301 and by about 2-4% Study 2302 (this difference was statistically significant by week in Study 2301 but not for Study 2302). Laxative use at each week averaged about 30% in the placebo group, about 25% in the 2 mg group and about 23% in the 6 mg group.

By week assessment of laxative use fails to give insight into the use by individual patients over the duration of drug exposure. Summing the laxative use over time (Table 3.8) reveals that more than 40% of the patients use no laxatives during the double-blind period. The median number of weeks of use is one week for all treatment arms. A Wilcoxon test on the number of weeks of laxative use showed a statistically significant difference between the 6 mg dose and placebo for Study 2301 (p=0.003) and borderline results for Study 2302 (p=0.06).

Table 3.8 Studies 2301 and 2302 Reviewer's Analysis

Number of weeks with laxative use during the double-blind treatment period

	Study 2301			**Study 2302**		
	PLA n=416	ZEL 2 n=417	ZEL 6 n=431	PLA n=447	ZEL 2 n=450	ZEL 6 n=451
# of wks w/ laxative use						
0	41%	45%	49%	40%	44%	48%
1	13%	11%	11%	14%	15%	12%
2	6%	10%	7%	8%	9%	8%
3	5%	7%	5%	7%	6%	5%
4	3%	5%	5%	7%	5%	4%
5	3%	4%	5%	3%	4%	4%
6	3%	4%	3%	3%	3%	2%
7	2%	1%	2%	3%	2%	3%
8	2%	2%	2%	4%	2%	3%
9	5%	2%	2%	2%	2%	2%
10	3%	2%	2%	2%	2%	3%
11	5%	3%	2%	2%	2%	2%
12	8%	5%	4%	4%	4%	5%

This reviewer also analyzed this laxative data by performing a weighted least squares, repeated measure analysis using logits on the data with the studies combined. This analysis allows one to use all the data over the 12-week period. Results of this analysis showed the following:

- The odds of using laxatives was significantly lower for the 6 mg dose group compared to placebo (p=.03); the 2 mg group was not significantly different from placebo.
- The odds of using a laxative decreased significantly over the 12 weeks for the 6 mg dose group but not for the 2 mg dose group or placebo.
- For the subgroup of patients who used laxatives at baseline, the odds of using laxatives was significantly lower for the 6 mg dose group (p=.01) and the 2 mg dose group (p=.01) compared to placebo.

Efficacy Results

This reviewer's analysis of efficacy focuses on the number of bowel movements since an improvement in number of bowel movements is the primary goal of Zelnorm therapy in a chronically constipated population and is of primary interest to the FDA medical review staff. The applicant's results for secondary endpoints (Appendix 4), not addressed in this review, showed statistically significant treatment effects in favor of Zelnorm over placebo.

Bowel movements were tabulated in three ways; total number of bowel movements (BM), number of complete spontaneous bowel movements (CSBM) and number of spontaneous bowel movements (SBM). CSBM was the primary outcome variable used to define responders. Patients with an average increase from baseline of 1 or more CSBM per week for the first four weeks of the study were considered responders for the primary endpoint. A secondary endpoint, patients with an average of 3 or more CSBM per week, was considered of greater importance to the FDA medical reviewer, Dr. Prizont. This reviewer examined both endpoints. In addition, this reviewer examined the CSBM's as a continuous variable (i.e. counts) to determine if the data underlying the responder data consistently showed results in favor of Zelnorm over placebo.

Statistical Methods

The primary population for analysis was the intent-to-treat (ITT), all patients randomized, population. Analyses were also performed using a per protocol population and a completer population.

For the primary endpoint, mean CSBM was computed as follows:

$$\text{CSBM/week} = 7 * \frac{\text{total \# of CSBM}}{\text{total number of days with data}}$$

Missing data were imputed with the average for the week in which the value was missing. So when there is missing diary data and at least one CSBM is recorded during the week, the imputed total weekly number of CSBM's will always be larger than the total observed CSBM's.

Baseline CSBM was computed as above; however, the total number of days was the total for the whole two week baseline period. For a patient with complete diary data, the total number of days would be 14. As for the weekly CSBM, missing days are imputed by the average of the available data. So baseline is not simply an average of the two weeks of baseline data but is based on available data with missing days imputed.

When computing monthly data or 12-week data, an average of the weekly CSBM for all available weeks was used and responder status was based on this average. So missing weeks are imputed using the average of the available weeks. For example, if a patient has 3 weeks of data for a given month, the 3 weekly total CSBM are averaged and responder status determined based on this average; so the fourth week is imputed by the average of the other 3 weeks. Note that being a responder for any given month does not imply that the patient is a responder at all 4 weeks; it merely implies that the patient responded for at least one week.

The applicant used a logistic regression model, with center, gender and baseline number of CSBM per week as independent variables, to analyze the responder data. Hochberg's procedure was used to adjust alpha levels for comparing both doses to placebo; if the largest of the two p-values is greater than 0.05, the second p-value must be equal to or smaller than 0.025 to be considered statistically significant.

This reviewer analyzed the data primarily using two procedures; the Cochran-Mantel-Haenszel chi square test for responder analyses and the Wilcoxon signed rank test for analyzing bowel movements as a continuous variable. Note that the results for the former were consistent with the results for the applicant's logistic regression model.

A total of 52 patients (18 placebo, 17 Zelnorm 2 mg and 17 Zelnorm 6 mg) without any double-blind data in the two studies were counted as nonresponders by the applicant but were generally not included in this reviewer's analyses. So for some analyses, this reviewer's denominators will differ from the applicant's. This difference between the analyses did not affect the interpretation of the results.

Applicant's Results

The applicant analyzed three responder variables; % of patients with an average increase of 1 or more CSBM per week, % of patients with an average of 3 or more CSBM per week and the % of patients with an average increase of 1 or more CSBM per week and with an average of 3 or more CSBM per week. Averages were computed for the first 4 weeks of the trial and for the entire 12 weeks of the trial. The protocol defined primary endpoint was the % of patients with an increase of 1 or more CSBM per week averaged over the first 4 weeks of the trial.

The applicant's results, summarized in Table 3.9, show statistically significant results for Zelnorm 6 mg versus placebo for all three endpoints, both during the first month and for the full 12 weeks. In Study 2301, a dose response relationship

is evident and non-significant results are seen for the 2 mg dose when looking at the data averaged over the full 12 weeks. For Study 2302, a dose response relationship is not evident for the two endpoints that consider the total number of CSBM/week.

Table 3.9 Applicant's results: percent of patients who are responders

	Study 2301			**Study 2302**		
	PLA n=416	ZEL 2 n=417	ZEL 6 n=431	PLA n=447	ZEL 2 n=450	ZEL 6 n=451
Weeks 1-4						
Inc≥1 CSBM/wk	26.7%	**35.6%**	**40.2%**	25.1%	**41.4%**	**43.2%**
≥3 CSBM/wk	12.9%	**18.8%**	**22.2%**	12.9%	**23%**	**21.8%**
Resp both	11.9%	**17.6%**	**21.0%**	11.3%	**22.7%**	**21.4%**
Weeks 1-12						
Inc≥1 CSBM/wk	30.6%	35.9%	**43.2%**	26.9%	**40.3%**	**44.8%**
≥3 CSBM/wk	14.3%	17.1%	**25.2%**	13.1%	**22.7%**	**22**%
Resp both	13.3%	15.9%	**24.1%**	12%	**22.3%**	**21.4%**

Bolded values are statistically significant versus placebo ($p<0.05$) determined by applying the Hochberg procedure. Source: [Summary of Clinical Efficacy - Table 3-15]

Reviewer's Results

The following issues regarding the applicant's responder analyses are addressed by this reviewer:

- effect of imputation
  - observed data
  - CSBM as a continuous measure
- use of only Month 1 data for the primary endpoint
  - Month 2, Month 3 and Week 12 data
  - responders for all 3 months
  - number of weeks responding

Results from Analysis of Observed Data

All the applicant's analyses are based on the CSBM normalized to 7 days as explained above. This can result in a CSBM total larger than the number actually observed if the patient is missing diary data. Of all the data collected about 3% of the normalized values are larger than the actual observed values; only about 1% are larger by 1 CSBM or greater. It is unlikely that the results will be greatly impacted by using this imputation method for computing CSBM because of the completeness of the diary data and the low dropout rates. Nevertheless, this reviewer has performed an analysis to check the robustness of the applicant's responder analysis by looking at the data as continuous and by using only the observed CSBM data for both baseline and response. Since patients have varying numbers of days on baseline and on treatment, a per day rate was calculated. Notice that an increase of 0.14 CSBM/day translates to an increase of about 1 CSBM per week and a mean CSBM of 0.28 is approximately 2 CSBM.

Table 3.10 Studies 2301 and 2302 Reviewer's Analysis
Mean daily rates of CSBM computed from the observed data

	Study 2301			**Study 2302**		
Time period	PLA n=416	ZEL 2 n=417	ZEL 6 n=431	PLA n=447	ZEL 2 n=450	ZEL 6 n=451
Baseline CSBM/day	(n=412)	(n=410)	(n=428)	(n=442)	(n=444)	(n=449)
Mean (SD)	0.070 (0.11)	0.078 (0.12)	0.076 (0.13)	0.085 (0.12)	0.078 (0.11)	0.083 (0.12)
Median	0	0	0	0	0	0
Weeks 1-4 CSBM/day	(n=406)	(n=403)	(n=420)	(n=431)	(n=436)	(n=439)
Mean (SD)	0.164 (0.22)	0.213 (0.29)	0.254 (0.31)	0.171 (0.25)	0.261 (0.33)	0.275 (0.36)
Median	0.071	0.107	0.143	0.071	0.143	0.179
CHANGE						
Mean (SD)	+0.09 (0.21)	**+0.14 (0.27)**	**+0.18 (0.27)**	+0.08 (0.22)	**+0.18 (0.30)**	**+0.19 (0.33)**
Median	0	**+0.04**	**+0.07**	+0.04	**+0.07**	**+0.11**
Weeks 5-8 CSBM/day	(n=375)	(n=379)	(n=388)	(n=402)	(n=417)	(n=409)
Mean (SD)	0.193 (0.27)	0.231 (0.32)	0.264 (0.31)	0.197 (0.28)	0.271 (0.32)	0.276 (0.31)
Median	0.071	0.115	0.143	0.073	0.143	0.179
CHANGE						
Mean (SD)	+0.12 (0.26)	+0.15 (0.30)	**+0.19 (0.29)**	+0.11 (0.26)	**+0.20 (0.30)**	**+0.19 (0.29)**
Median	+0.02	+0.07	**+0.11**	+0.04	**+0.07**	**+0.11**
Weeks 9-12 CSBM/day	(n=349)	(n=350)	(n=369)	(n=371)	(n=389)	(n=385)
Mean (SD)	0.197 (0.27)	0.232 (0.30)	0.289 (0.36)	0.210 (0.27)	0.267 (0.32)	0.282 (0.31)
Median	0.071	0.107	0.179	0.107	0.142	0.20
CHANGE						
Mean (SD)	+0.13 (0.25)	+0.15 (0.30)	**+0.22 (0.34)**	+0.12 (0.25)	**+0.19 (0.30)**	**+0.20 (0.30)**
Median	+0.04	+0.04	**+0.10**	+0.04	**+0.07**	**+0.11**
Weeks 1-12 CSBM/day	(n=407)	(n=403)	(n=420)	(n=431)	(n=437)	(n=440)
Mean (SD)	0.180 (0.23)	0.224 (0.29)	0.265 (0.29)	0.187 (0.25)	0.270 (0.32)	0.275 (0.30)
Median	0.08	0.13	0.167	0.095	0.167	0.196
CHANGE						
Mean (SD)	+0.11 (0.21)	**+0.15 (0.27)**	**+0.19 (0.26)**	+0.10 (0.22)	**+0.19 (0.30)**	**+0.19 (0.28)**
Median	+0.04	**+0.06**	**+0.11**	+0.04	**+0.09**	**+0.11**

Mean change from baseline values significantly different from placebo are bolded. Results are based on a Wilcoxon test applying Hochberg's multiple comparison adjustment.

These results (Table 3.10) of the observed data analyzed as continuos data support the applicant's responder results; consistent significant treatment effects for the 6 mg dose compared to placebo are seen at each month and for the duration of the trial. No dose response is seen in Study 2302; in Study 2301, the 2 mg dose is not significantly different from placebo at Months 2 and 3.

The average increase per week is about 1.3 CSBM (median of 0.8) for Zelnorm 6 mg compared to an average increase of 0.7 CSBM (median of 0.3) for placebo; so the average treatment effect is an increase less than 1 CSBM/week. Another way to summarize the effect is that a Zelnorm 6 mg patient needs an average of approximately 10-11 days to experience 3 CSBM. This result is consistent with the applicant's analysis of time to first CSBM where the median time to first CSBM for Zelnorm 6 mg was about 3-4 days. So the overall data suggests that the time between CSBM does not shorten with continued Zelnorm treatment. Note that these Zelnorm 6 mg values are all

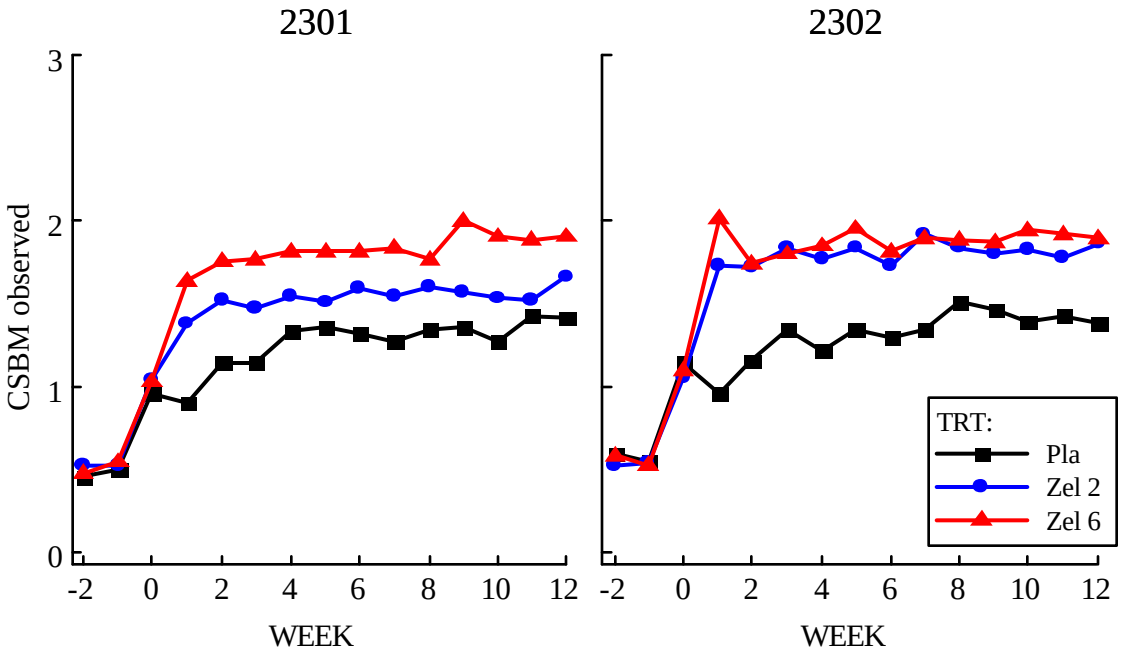
statistically significantly different from placebo but perhaps of questionable clinical significance.

By Month Results

The applicant focussed on responder analyses of the first month and the full 12 weeks; the latter included all patients regardless of how many weeks of data a patient had.

A graph of the mean CSBM over time (Figure 3.2) clearly shows that the largest differences between drug and placebo are seen during the early weeks of the trial with the placebo response maximized at about Week 4. So analysis of the first 4 weeks of data would maximize the treatment difference. Plots of total BM and SBM (Appendix 5) show a similar pattern of response.

Figure 3.2 Mean CSBM (observed values, not imputed) by week, treatment group and study



The overall CSBM data is also presented in Appendix 6 where the percent of patients by number of weekly CSBM is shown by treatment and week. The percentages show the largest treatment differences in distribution of CSBM during the early weeks. For example, at Week 1, the percentage of patients with 3 or more CSBM is 27% for Zelnorm 6 mg and 12% for placebo (a difference of 15%). At Week 8, the percentage of patients with 3 or more CSBM is 30% for Zelnorm 6 mg and 23% for placebo (a difference of 7%).

To determine if the responder results seen at Month 1 are also observed at Months 2 and 3, this reviewer analyzed the available data at each of those subsequent months. For the 6 mg dose, significant treatment effects are seen at each month for both responder variables. Though the magnitude of the response for the 2 mg dose is greater

than placebo, the results at Months 2 and 3 do not show significant results over placebo in Study 2301.

Table 3.11 Studies 2301 and 2302 Reviewer's Analysis
Responders for 4-week intervals where responder is defined as a patient having a mean increase of ≥ 1 CSBM/week or having a mean of ≥ 3 CSBM/week

	Study 2301			**Study 2302**		
	PLA n=416	ZEL 2 n=417	ZEL 6 n=431	PLA n=447	ZEL 2 n=450	ZEL 6 n=451
Weeks 1-4						
Inc≥1 CSBM/wk	28% (112/406)	**36%** (146/403)	**42%** (176/420)	26% (113/431)	**42%** (185/436)	**45%** (197/439)
≥3 CSBM/wk	13% (53/409)	**19%** (79/409)	**23%** (96/423)	14% (60/433)	**23%** (102/440)	**24%** (104/441)
Weeks 5-8						
Inc≥1 CSBM/wk	33% (122/375)	38% (143/379)	**44%** (172/388)	31% (124/405)	**43%** (178/417)	**47%** (192/409)
≥3 CSBM/wk	17% (64/376)	20% (76/385)	**26%** (101/390)	17% (68/404)	**26%** (110/421)	**27%** (112/411)
Weeks 9-12						
Inc≥1 CSBM/wk	33% (116/349)	39% (135/350)	**44%** (162/369)	32% (120/371)	**41%** (160/389)	**45%** (174/385)
≥3 CSBM/wk	19% (66/351)	21% (73/355)	**28%** (105/371)	18% (69/374)	**25%** (99/393)	**28%** (108/387)
Respond all 3 months						
All pts						
Inc≥1 CSBM/wk	15% (60/411)	**20%** (83/409)	**24%** (102/423)	15% (64/434)	**24%** (107/441)	**26%** (113/442)
≥3 CSBM/wk	8% (31/411)	10% (39/409)	**12%** (52/423)	7% (31/434)	**14%** (61/441)	**12%** (61/441)
Completers						
Inc≥1 CSBM/wk	17% (60/347)	24% (83/350)	**28%** (102/368)	17% (64/369)	**28%** (107/387)	**30%** (113/383)
≥3 CSBM/wk	9% (31/348)	11% (39/355)	**14%** (52/370)	8% (31/371)	**16%** (61/391)	**14%** (52/385)
Respond for at least 1 month						
Inc≥1 CSBM/wk	44% (181/411)	51% (207/409)	**57%** (239/423)	42% (182/434)	**55%** (244/441)	**60%** (266/442)
≥3 CSBM/wk	23% (93/411)	**29%** (120/409)	**36%** (151/423)	24% (106/434)	**33%** (147/441)	**38%** (169/442)

Bolded values indicate that the results were significantly different from placebo at p<0.02; bolded and shaded indicates significance at a level between 0.02 and 0.05.

The percentage of patients responding for all 3 months is small at about half the monthly rates; though the rates for Zelnorm 6 mg are statistically significantly larger than placebo.

The above analysis looks at the data by month; so averages are computed based on four weeks of data [for example, a patient may have a large response at one week and not at the other 3 weeks but yet average out as a monthly responder]. We could look at response by week and determine how often patients respond by week. The medical reviewer, Dr. Prizont, was particularly

interested in knowing how often patients had 3 or more CSBM per week. To look at this issue, this reviewer counted the number of weeks a patient had 3 or more CSBM. The average number of weeks is summarized in Table 3.12 below for all patients and for completers. Looking at the data this way, we can see that about half the patients are either responders at only one week or not at any week. These numbers are consistent with the low responder rates seen for the by month analysis where only about 26% of the patients on the high dose had an average of 3 or more CSBM for any given month.

Table 3.12 Studies 2301 and 2302 Reviewer's Analysis
Number of weeks with 3 or more CSBM

	Study 2301			**Study 2302**		
	PLA n=416	ZEL 2 n=417	ZEL 6 n=431	PLA n=447	ZEL 2 n=450	ZEL 6 n=451
All patients						
Mean (SD)	2.2 (3.3)	2.6 (3.5)	3.2 (3.9)	2.2 (3.2)	3.1 (3.9)	3.3 (3.7)
Median	0	1	1	0	1	2
Range	0-12	0-12	0-12	0-12	0-12	0-12
Completers						
Mean (SD)	2.4 (3.3)	2.9 (3.7)	3.6 (4.1)	2.5 (3.4)	3.5 (4.0)	3.8 (3.8)
Median	0	1	2	1	2	3
Range	0-12	0-12	0-12	0-12	0-12	0-12
# of wks w/ 3 or more CSBM						
0	52.6%	46.7%	40.2%	51.6%	38.3%	34.8%
1	12.2%	10%	10.9%	10.8%	14.5%	13.6%
2	7.3%	7.3%	6.4%	6.5%	8.2%	5.9%
3	4.6%	6.1%	6.9%	7.1%	5.7%	7%
4	4.6%	5.6%	4.5%	5.1%	3.2%	5.7%
5	3.9%	3.9%	4.0%	3.7%	5.2%	5.4%
6	1.5%	3.7%	3.5%	1.8%	4.3%	6.8%
7	1.7%	3.4%	4.5%	3.0%	2.7%	4.3%
8	2.2%	2.7%	3.1%	2.5%	4.1%	4.3%
9	2.9%	3.4%	3.3%	2.8%	1.6%	2.5%
10	2.4%	1.2%	4.3%	1.2%	3.4%	3.2%
11	1%	2.4%	3.8%	2.1%	3.9%	3.6%
12	3.2%	3.4%	4.7%	1.8%	5%	2.9%

As seen by the means in Table 3.12, completers are responders at more weeks than the overall population. This is not surprising since one would expect patients with good responses would stay on trial longer. A cumulative distribution plot of number of weeks with 3 or more CSBM for completers (Appendix 7) illustrates the treatment difference.

Week 12 Results

The FDA medical reviewer, Dr. Prizont, was interested in the treatment effect at the end of the trial, Week 12. Only patients with Week 12 data are used in this analysis; so there is no carrying forward of data from earlier weeks for this analysis. Most of the patients on study at Week 12 have complete data (Table 3.13).

The treatment effect for the 6 mg dose of Zelnorm is statistically significantly different from placebo regardless of the measure used to assess efficacy (Table 3.13). Consistent with other analyses, the 2 mg dose response results are similar to the 6 mg dose in Study 2302 and not significant in Study 2301.

Table 3.13 Reviewer's CSBM Week 12 Results for Completers

	Study 2301			**Study 2302**		
	PLA n=337	ZEL 2 n=343	ZEL 6 n=350	PLA n=353	ZEL 2 n=377	ZEL 6 n=367
Days w/data during Wk 12						
7 days	89%	88%	87%	89%	86%	87%
6 days	5%	7%	7%	4%	6%	5%
5 days	4%	1%	2%	5%	4%	3%
1-4 days	2%	3%	4%	2%	4%	5%
Baseline CSBM	0.5 (0.7)	0.6 (0.9)	0.5 (0.8)	0.6 (0.9)	0.5 (0.8)	0.6 (0.8)
Week 12 CSBM						
Mean (SD)	1.5 (2.2)	1.7 (2.5)	**2.0 (2.5)**	1.4 (2.2)	**1.9 (2.6)**	**2.0 (2.5)**
Median	0	0	**1.0**	0	**1.0**	**1.0**
Change						
Mean (SD)	+1.0 (2.0)	+1.2 (2.4)	**+1.4 (2.4)**	+0.8 (2.2)	**+1.4 (2.4)**	**+1.4 (2.4)**
Median	0	0	**+0.5**	0	**0**	**+0.5**
% w/ch≥1	37%	39%	**46%**	33%	**45%**	**45%**
% w/CSBM≥3	23%	29%[3]	**32%**	21%	**31%**	**33%**
% w/both	22%	28%	**32%**	19%	**31%**	**30%**

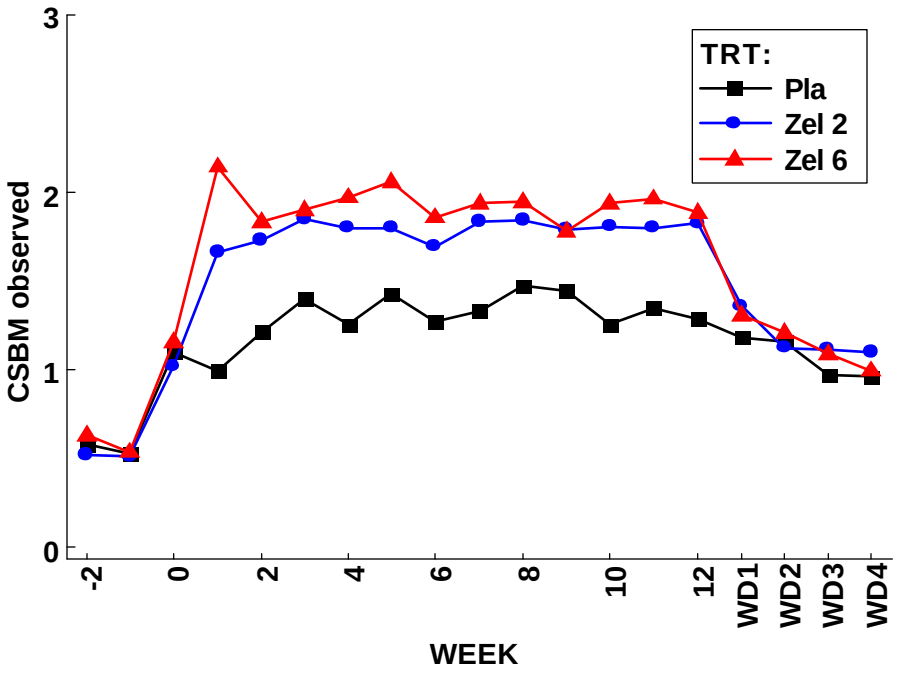
Withdrawal of drug in Study 2302

In Study 2302, patients who completed the study had the drug withdrawn and were followed for an additional 4 weeks. According to the applicant "the percentage of responders rapidly decreased in both Zelnorm groups to reach the level of the placebo group in 2 weeks after termination of the treatment." Appendix 3 of this review illustrates the increase in laxative use during withdrawal in all treatment groups, including placebo. Appendix 6 illustrates the shift in the distribution of CSBM during withdrawal and again all three treatment

3 p=0.05 unadjusted for multiple comparisons

groups show a decrease in number of CSBM such that at the last week of withdrawal, 83% of the Zelnorm 6 mg and 85% of the placebo patients have fewer than 3 CSBM. The graph on the next page shows the observed CSBM for those patients who completed the withdrawal phase (about 72% of the randomized patients). A drop in CSBM in the Zelnorm groups is clearly evident at the visit one week after drug withdrawal.

Figure 3.3 Mean CSBM (observed) for patients who completed the withdrawal period



3.1.2 Extension Study 2301E1

Study 2301E1 is a 13-month double-blind extension of Study 2301. Patients being treated with Zelnorm continued on their same dose while placebo patients were switched to Zelnorm 6 mg BID; the blind was maintained until the end of the extension period though patients were aware that all patients would be receiving Zelnorm. The primary objective of this trial was to collect long-term safety data. Patients kept monthly diaries where a log of ADE's and concomitant medication use was recorded and where bowel habits were assessed for the last week of the month using the four questions shown in Appendix 1 of this review plus "How many bowel movements did you have in the past week?". So total number of bowel movements was collected for one week out of each month without distinguishing spontaneous from non-spontaneous bowel movements. QOL data was collected at Months 13 and 16 and at discontinuation.

About 99% of the patients who completed Study 2301 were enrolled in Study 2301E1. There were a total of 842 patients in the extension phase; 282 on

Zelnorm 2 mg BID and a total of 558 patients on Zelnorm 6 mg BID (Table 3.14 on the following page). A little more than half of these patients completed Study 2301E1. The major reason for discontinuing was lack of efficacy and was about the same in each group (Table 3.14).

Table 3.14 Study 2301E1 Patient disposition

	Zel 2 mg	Zel 6 mg	Plac/Zel 6 mg
Enrolled	284	283	275
Discontinuations			
ADE	20 (7%)	14 (5%)	19 (7%)
LOE	56 (20%)	51 (18%)	55 (20%)
Pt req	31 (11%)	30 (11%)	31 (11%)
Other	23 (8%)	30 (11%)	31 (11%)
Completed	154 (54%)	158 (56%)	139 (51%)

The applicant provided graphs showing discontinuations over time (Figures 7-1a, b and c on pages 37-38 of the study report) and so it was possible to estimate the percentage of dropouts at Week 12 in the placebo/Zelnorm group and compare those rates to the 6 mg rates seen in Study 2301 at Week 12. It is interesting that 4 times as many patients who switched from placebo to Zelnorm 6 mg dropped due to lack of efficacy than patients originally randomized to Zelnorm 6 mg in Study 2301. On the other hand, the ADE rates are lower for the Placebo/Zelnorm patients.

Table 3.15 Comparison of Study 2301 dropouts and 2301E1 dropouts in patients on 6 mg after ~12 weeks of treatment

	Study 2301 Zel 6 mg	Study 2301E1 Plac/Zel 6 mg
Enrolled	431	275
Discontinuations		
ADE	8%	~4%
LOE	3%	~12%

Overall the dropout rate for about a total of 15 months of therapy was very high; only about 37% of the patients originally randomized to Zelnorm treatment completed the extension study. For patients randomized to placebo and then switched to Zelnorm 6 mg, the overall completion rate was lower at 33%.

The demographics of the patients were similar to those seen for the core Study 2301.

The median exposure to the 6 mg dose was 365 days (range of 10 to 530 days).

About 2-3% of the patients took laxatives other than bisacodyl. Use of bisacodyl continued to be high with 63%, 60% and 31% of the Zelnorm 2, Zelnorm 6 and Placebo/Zelnorm 6, respectively, taking laxatives at some time during the extension phase. It is not clear why laxative use in the patients switching treatment to Zelnorm is so low; this reviewer will examine this in a future document.

From the applicant's summary of the laxative data and of the bowel movement data, it was not clear to this reviewer how patients fared with long-term use of Zelnorm. It is not possible to discern from the applicant's presentations any trends in laxative use or whether the patients' bowel movements stabilized or continued to increase independent of laxative use. Due to the time constraints on this review and problems with interpretation of some of the variables in the datasets for this study, this reviewer was

not able to further investigate these issues but plans to address them in a final version of this review.

3.2 Evaluation of Safety

The safety data was reviewed by Dr. Gary Della'Zanna (FDA medical reviewer in HFD-180). Statistical input was provided by Dr. Ted Guo (statistical reviewer in DB2).

4. Findings in Special/Subgroup Populations

The usual goal of subgroup analyses is to show consistency of the treatment effect across selected subgroups; the exception would be the case where the applicant is seeking an indication in a subgroup, in which case, a significant treatment effect in that subgroup would be necessary. Consistency may be demonstrated by running tests of interaction between treatment and the subgroup variable. This reviewer performed tests of interaction using a logistic regression model including as main effects, treatment and the subgroup variable with the interaction term. This model was run for studies separately and pooled; only the pooled results are presented. Only significant interactions ($p<0.10$) are mentioned.

The results for two responder variables are presented for each subgroup; 1) the primary endpoint, a mean increase of 1 or more CSBM per week during the first 4 weeks of the trial, and 2) an endpoint created by this reviewer, a mean of 3 or more observed CSBM per week for the duration of the trial.

The overall results and by study results for the two responder endpoints are provided in Table 4.1 as reference for the subgroup analyses presented below.

Table 4.1 Percentage of responders for the studies combined and separately

	PLA	ZEL 2	ZEL 6
Inc[3] 1 CSBM/wk Wks 1-4			
All patients	26% (221/863)	38% (330/867)	42% (366/882)
Study 2301	26% (110/416)	35% (146/417)	40% (172/431)
Study 2302	25% (111/447)	41% (184/450)	43% (194/451)
[3] 3 obs. CSBM/wk All wks			
All patients	14% (120/845)	20% (172/850)	25% (212/865)
Study 2301	14% (59/411)	17% (70/409)	26% (109/423)
Study 2302	14% (61/434)	23% (102/441)	23% (103/442)

4.1 Gender, Race and Age

About 91% of the patients in the two studies are Caucasian, so there are insufficient number of patients of other races to perform subgroup analyses based on race.

Most of the study population was females (about 88%). The interaction effect for treatment by gender is borderline significant (p=0.11); it is clearly a quantitative interaction with males showing a higher response rate across all three treatment groups and a smaller treatment effect (Table 4.2). The reviewing division is considering an indication for females only, because of the under-representation of males in the study and also, because the trial population may not represent patients with functional/idiopathic constipation; the primary type of constipation seen in males. Due to the latter, this reviewer computed p-values by gender and found highly significant results for Zelnorm 2 mg and 6 mg over placebo for females but nonsignificant results for males.

The applicant reported a treatment by age interaction (p=.0437) and noted that the interaction was due to a higher placebo responder rate seen in older patients. This reviewer looked at various age cutpoints and found significant interactions for cutpoints of 46 (the median) and 65 but not for 60 (p>0.19); nevertheless, regardless of the cutpoint, treatment effects for the older subgroup is generally less than half the effect seen for the younger subgroup. This is problematic if Zelnorm is used predominantly by an elderly population.

Table 4.2 Percentage of responders by gender and age

	PLA	ZEL 2	ZEL 6
GENDER			
Inc ≥ 1 CSBM/wk Wks 1-4			
Females	25% (190/770)	38% (287/759)	42% (324/775)
Males	33% (31/93)	40% (43/108)	39% (42/107)
≥ 3 obs CSBM/wk All wks			
Females	14% (102/752)	20% (146/743)	24% (182/759)
Males	19% (18/93)	24% (26/107)	28% (30/106)
AGE			
Inc ≥ 1 CSBM/wk Wks 1-4			
Age (years)			
≤46 (Median)	21% (94/451)	36% (158/435)	42% (188/448)
>46	31% (127/412)	40% (172/432)	41% (178/434)
<60	25% (170/679)	39% (310/727)	43% (310/727)
≥60	28% (51/184)	35% (57/165)	36% (56/155)
<65	25% (184/745)	39% (286/742)	42% (337/794)
≥65	31% (37/118)	35% (44/125)	33% (29/88)
≥ 3 obs CSBM/wk All wks			
≤46 (Median)	13% (57/439)	19% (82/423)	25% (110/438)
>46	16% (63/406)	21% (90/427)	24% (102/427)
<60	14% (91/661)	20% (136/686)	25% (179/712)
≥60	16% (29/184)	22% (36/164)	22% (33/153)
<65	13% (98/727)	20% (145/726)	25% (194/779)
≥65	19% (22/118)	22% (27/128)	21% (18/86)

4.2 Other Special/Subgroup Populations

Applicant's analyses of subgroups defined by entry criteria

At a pre-sNDA meeting, FDA questioned the entry criteria for the two completed clinical trials and asked for additional analyses to show results based on 1) selection of patients using spontaneous bowel movements instead of CSBM and 2) exclusion of patients based on IBS-like characteristics at baseline. The applicant's results discussed here are presented in detail in Section 2.7.3 Addendum to Summary of Clinical Efficacy in Chronic Constipation of the NDA. This reviewer had not replicated the applicant's analyses at the time of the completion of this review because the applicant had not yet provided requested coding for variables needed to perform the analysis.

Approximately 42% of the patients met the FDA recommended constipation criteria based on spontaneous bowel movements. Results of subgroup analyses

for all 4 of the main responder variables (increase of 1 or more in CSBM at the first month and for all 12 weeks and average of 3 or more CSBM per week at the first month and for all 12 weeks) showed statistically significant treatment effects ($p<.0001$) for the 6 mg dose over placebo for patients meeting and for patients not meeting the revised criteria. The results for the 2 mg dose were more variable with nonsignificant results seen for some endpoints.

Approximately 23% of the patients presented with IBS-like symptoms. IBS-like symptoms were defined as any of the following (not exclusive):

1. Diagnosis of IBS (3%)
2. Abdominal discomfort as main complaint (12%)
3. Bothersome abdominal pain with diarrhea (10%)

Exclusion of the data for these IBS-like patients from an analysis did not appreciably change the results for the 4 responder variables; all comparisons to placebo were highly significant ($p<0.0001$) for both doses (see Appendix 8 for a summary of the applicant's results); responder rates for the non-IBS-like patients were similar to the overall rates.. Responder rates for patients with IBS-like symptoms were generally lower than the rates for the non-IBS-like patients and usually were not significantly different from placebo; however, for all 4 variables the IBS-like responder rates for Zelnorm were greater, numerically, than the placebo rates.

Subgroups by baseline CSBM and baseline SBM

In general, increasing response rates in all treatment groups are seen with increasing baseline values of CSBM and SBM. This is not surprising considering that patients with no baseline CSBM or no baseline SBM may be a more difficult population to treat. Notice, on the other hand, that the treatment effects are quite consistent (the last column of Table 4.3) taking into consideration the variability of the sample sizes.

A test of homogeneity showed the results were consistent across subgroups defined by CSBM and SBM for both variables. Treatment effects adjusted for baseline are highly significant with $p<.0001$ for both doses.

Patients with 3 or more CSBM are protocol violators; dropping those patients from the analyses of both variables for each study reveals that the results are still highly significant with $p<.0004$.

Table 4.3 Percentage of responders by baseline CSBM and baseline SBM

	PLA	ZEL 2	ZEL 6	ZEL 6 - PLA
Inc[3] 1 CSBM/wk Wks 1-4				
By Baseline CSBM				
0	23% (143/618)	36% (225/629)	39% (251/647)	+16%
1	34% (56/164)	42% (65/153)	52% (74/143)	+18%
2	36% (20/56)	58% (30/52)	49% (33/68)	+12%
3 or more	13% (2/16)	50% (10/20)	42% (8/19)	+29%
By Baseline SBM				
0	13% (19/148)	25% (35/138)	31% (49/160)	+18%
1	28% (45/159)	38% (67/175)	44% (73/167)	+16%
2	35% (50/143)	45% (63/139)	42% (64/154)	+7%
3	30% (36/121)	41% (54/131)	51% (60/117)	+21%
4 or more	25% (71/283)	41% (111/271)	43% (120/279)	+18%
[3] **3 obs CSBM/wk All wks**				
By Baseline CSBM				
0	7% (45/605)	15% (91/619)	18% (112/635)	+11%
1	24% (39/162)	26% (38/149)	36% (51/140)	+12%
2	49% (27/55)	58% (30/52)	50% (33/66)	+1%
3 or more	44% (7/16)	65% (13/20)	74% (14/19)	+30%
By Baseline SBM				
0	4% (6/144)	10% (13/135)	10% (16/155)	+6%
1	14% (21/155)	14% (24/171)	19% (31/162)	+5%
2	14% (20/141)	26% (36/136)	26% (40/153)	+12%
3	14% (16/118)	22% (28/129)	31% (36/116)	+17%
4 or more	20% (55/280)	26% (71/269)	32% (87/274)	+12%

Subgroups by laxative use

As already mentioned in this review, about half the patients had a history of laxative use before enrollment and about half used laxatives at baseline. About 70% of the patients used rescue medication (laxative bisacodyl, 5-15 mg per day) during baseline and/or during double blind treatment; so about 1/3 of the patients had no laxative use at all while on study. Use of concomitant medications that affect bowel habits was not permitted on trial; however, a small percentage of patients took psyllium (<1%) or used bulk producers (<3%).

Since laxative use on study differed between trials, this reviewer analyzed the laxative-use subgroup data by study.

The results by baseline use of laxatives generally show significantly higher responder rates for the Zelnorm groups compared to placebo regardless of use (Table 4.4); all tests of homogeneity for the 6 mg dose versus placebo were non-significant showing that treatments effects were similar for both subgroups.

Patients who did not use laxatives at all during the study showed higher response rates across all the treatment groups than was seen for the overall groups (see Table 4.1 for comparison). Comparisons of the 6 mg dose to placebo showed no statistically significant effects in Study 2301 (both variables, p~0.10) while in Study 2302 , the results were statistically significant.

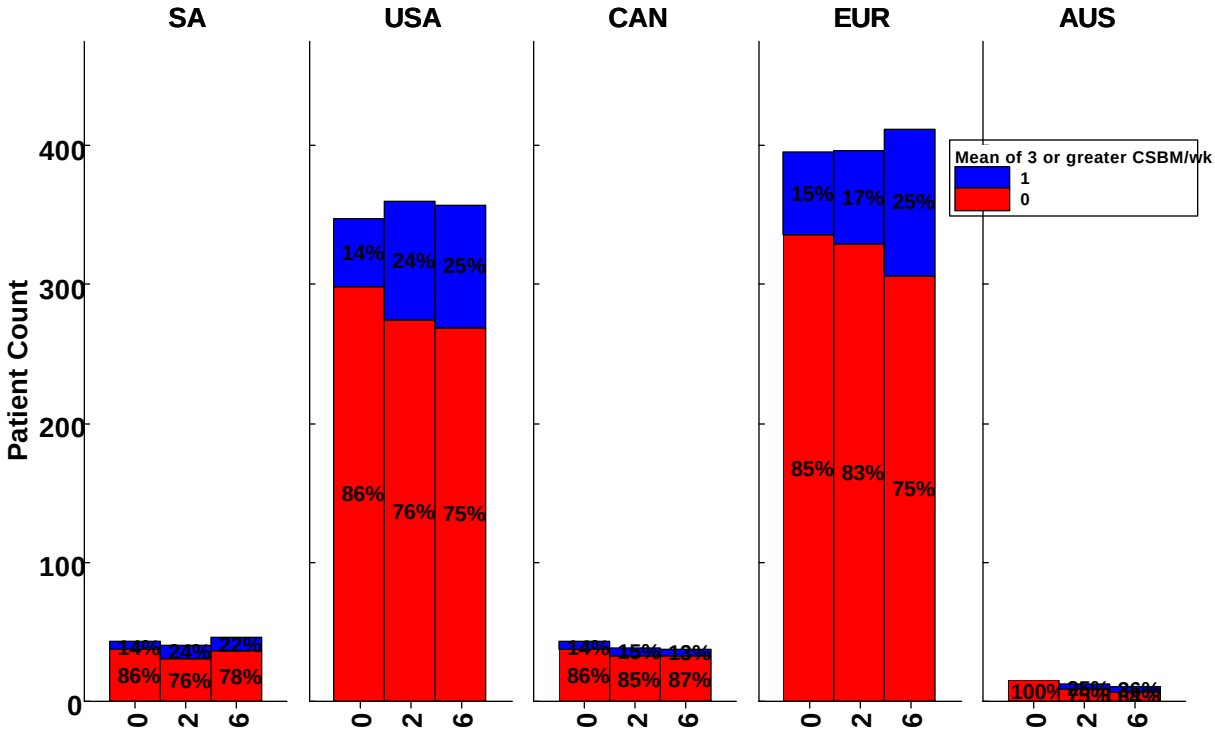
Table 4.4 Percentage of responders by baseline laxative use and for patients with no laxative use

	Study 2301			Study 2302		
	PLA n=416	ZEL 2 n=417	ZEL 6 n=431	PLA n=447	ZEL 2 n=450	ZEL 6 n=451
Inc[3] 1 CSBM/wk Wks 1-4						
Baseline lax. use						
Yes	22% (49/220)	33% (72/221)	39% (91/231)	26% (57/219)	37% (86/231)	43% (102/239)
No	31% (61/196)	38% (74/196)	41% (81/200)	24% (54/228)	45% (98/219)	43% (92/212)
No laxative use at baseline+DB trt	39% (48/122)	45% (57/128)	48% (70/146)	31% (40/131)	51% (71/139)	47% (70/149)
[3] 3 obs CSBM/wk All wks						
Baseline lax. use						
Yes	9% (20/218)	13% (28/217)	21% (48/225)	12% (25/214)	20% (45/227)	18% (43/236)
No	20% (39/193)	22% (42/192)	31% (61/198)	16% (36/220)	27% (57/214)	29% (60/206)
No laxative use at baseline+DB trt	27% (33/122)	29% (37/128)	37% (54/146)	24% (32/131)	31% (43/139)	36% (53/149)

Subgroups by geographical location of sites

The two trials were primarily conducted in Europe (2301) and the USA (2302) as can be seen from the patient numbers in Figure 4.1 and so the results for those areas are consistent with the overall results of the trials.

Figure 4.1 Percentage of patients with an average of 3 or more CSBM per week (in blue) for the duration of the trial by treatment and by geographic area



Subgroups by main complaint during the 6 months prior to screening

At the time of screening, patients were asked for their main constipation complaint during the preceding 6 months with the following:

Subject's main complaint in the preceding 6 months:
(please mark only one box)

- ☐ **1** Straining
- ☐ **2** Abdominal pain
- ☐ **3** Abdominal distension/bloating
- ☐ **4** Infrequent defecation
- ☐ **5** Feeling of incomplete evacuation
- ☐ **6** Hard stools
- ☐ **88** Other *(specify)* _____.

The majority of patients (>98%) responded with one of the first 6 choices. The most frequent complaints were abdominal distension/bloating (28%) and infrequent defecation (21%). The distributions of baseline number of CSBM and SBM (Appendix 9) show that the groups are similar regarding CSBM but that the median SBM for patients complaining of infrequent defecation is slightly lower than the medians for the other subgroups suggesting the observed data supports the subjective complaint of infrequent defecation.

The medical reviewer, Dr. Prizont, considered the patient's primary complaint to be a strong indication of the disease underlying the constipation. For example, patients' with a primary complaint of abdominal pain (about 12%) may have constipation-IBS. So it is important to look at efficacy responses by the main complaint at screening.

The response rates and treatment effects are similar to the overall rates for all the subgroups except for those patients complaining of abdominal pain (Table 4.5) where the treatment effects for the 6 mg dose over placebo is less than half the effect seen for the other 5 subgroups. It is also interesting to note that the 2 mg dose shows a numerically higher responder rate than the 6 mg dose for patients complaining of abdominal pain.

Table 4.5 Percentage of responders by main constipation complaint at screening

Main Complaint for 6 mos prior to randomization	PLA	ZEL 2	ZEL 6	ZEL 6 - PLA
Inc[3] 1 CSBM/wk Wks 1-4				
Abd. distension/bloat.	25% (60/239)	37% (90/245)	40% (99/246)	+15%
Infrequent defecation	18% (31/172)	42% (78/185)	44% (82/188)	+16%
Abdominal pain	25% (26/102)	32% (35/108)	30% (33/109)	**+5%**
Incompl. evacuation	25% (34/135)	32% (38/118)	41% (49/119)	+16%
Straining	36% (41/113)	44% (47/108)	49% (53/108)	+13%
Hard stools	26% (24/92)	38% (41/99)	44% (44/101)	+18%
[3] **3 CSBM/wk All wks**				
Abd. distension/bloat.	10% (24/235)	19% (46/237)	20% (49/242)	+10%
Infrequent defecation	12% (20/167)	20% (37/181)	23% (43/185)	+11%
Abdominal pain	14% (14/102)	19% (20/107)	18% (19/106)	**+4%**
Incompl. evacuation	17% (22/133)	18% (21/116)	29% (33/115)	+12%
Straining	23% (26/112)	25% (26/106)	36% (38/105)	+13%
Hard stools	13% (11/87)	20% (20/99)	29% (29/101)	+16%

Subgroups by length of time of constipation (years)

The median length of time that patients reported having constipation was 12 years for both studies combined so 12 was used as a cutoff value to define the subgroups (Table 4.6). The responder rates are smaller in the patients with a longer history of constipation by about 3-4% across all treatment groups; however, the treatment effects are the same regardless of length of time of constipation reported at baseline. The treatment effect for the 6 mg dose is about 15% for the applicant's primary endpoint and about 10% for the percent of patient with 3 or more CSBM/week (the FDA review division's preferred endpoint) in both subgroups.

Table 4.6 Percentage of responders by the years of constipation

Years of constipation	PLA	ZEL 2	ZEL 6
Inc[3] 1 CSBM/wk Wks 1-4			
By median time			
≤12 years	28% (119/432)	40% (174/440)	43% (192/451)
> 12 years	24% (102/430)	37% (156/426)	40% (174/431)
[3] **3 CSBM/wk All wks**			
By median time			
≤12 years	16% (68/423)	22% (93/432)	27% (118/442)
>12 years	12% (52/421)	19% (79/417)	22% (94/423)

5. Summary and Conclusions

5.1 Statistical Issues

There were two major issues in Studies 2301 and 2302. The first issue was the selection of patients for the trials. The medical reviewer, Dr. Prizont, was concerned that the population studied was not representative of patients with functional/idiopathic constipation, "the most common form of constipation" (Dr. Prizont's review). Prevalence of functional/idiopathic constipation is highest among the elderly and equally likely in males and females; however, both the elderly (~13%) and men (~12%) were under-represented in both studies. In addition, the medical reviewer was concerned that patients in these studies were not screened for IBS (Zelnorm is already approved for constipation-IBS). To address the question of whether the results may be generalized to patients with characteristics of functional/idiopathic constipation, this reviewer performed analyses of subgroups defined by age, gender, baseline bowel movements and presenting constipation complaint. Also included in the review are analyses performed by the applicant of subgroups defined by entry criteria and IBS-like symptoms.

The second major issue of concern was the definition of the primary endpoint. These concerns were both clinical and statistical. The primary endpoint was a responder endpoint where responders were defined as patients with a mean decrease of one or more CSBM per week averaged over the first 4 weeks of the trial. The clinical concern expressed by the medical reviewer, Dr. Prizont, was that patients could remain constipated by definition (fewer than 3 CSBM/week)

but yet be considered responders. This latter concern was addressed in two ways in this review; 1) analysis of a protocol-specified secondary variable where responders are patients with 3 or more CSBM per week and 2) subgroup analyses based on baseline CSBM to determine if patients with no CSBM or only 1 CSBM show benefit from Zelnorm treatment.

Additional statistical concerns regarding the primary endpoint which were addressed in the review included the following:

- use of imputed data by the applicant versus observed data
- choice of week as the unit of measurement
  - the analysis of the first 4 weeks as the primary outcome

Other statistical issues included the observation of a large placebo response and the impact of rescue medication on efficacy; the latter was of particular concern since laxative use was high and patients remained on study regardless of laxative use.

5.2 Collective Evidence and Conclusions

The applicant has presented the results of two clinical trials; 2301, predominantly a European study and 2302, predominantly a USA study. Most of the patients were female, under 65 years old and Caucasian and had a long history of constipation (Table 3.4). About 60% of the patients had a history of laxative use and about 53% used laxatives during the 2-week baseline period. At screening, the main constipation complaints reported by about half the patients were abdominal distension/bloating or infrequent defecation. Less than 5% of the patients entered the trial with a diagnosis of IBS though about ? of the patients exhibited IBS-like symptoms.

During the baseline period, patients had an average of 4 bowel movements per week; on average 3 of the BM's were spontaneous and none were complete (Table 3.5). So about half the patients had no CSBM at baseline and about half of the patients recorded fewer than 3 spontaneous (complete+incomplete) bowel movements. The latter is part of a common definition for constipation (see Dr. Prizont's review for more details).

Table 5.1 below summarizes the results for the primary efficacy variable (responder defined as a patient having a mean increase of ≥ 1 CSBM/week for the first 4 weeks of the study) and for the FDA medical division's preferred efficacy variable (responder defined as a patient having a mean of ≥ 3 CSBM/week). Results for the first month showed statistically significant treatment effects for both doses of Zelnorm versus placebo with a dose response relationship evident for Study 2301 but not for Study 2302. Analyses for Months 2 and 3 showed significant treatment effects for Zelnorm 6

mg versus placebo in both studies but no significant results for Zelnorm 2 mg in Study 2301.

5.1 Percentage of responders for the first month (primary endpoint) and percentage of patients responding for all three months

	Study 2301			**Study 2302**		
	PLA n=416	ZEL 2 n=417	ZEL 6 n=431	PLA n=447	ZEL 2 n=450	ZEL 6 n=451
Weeks 1-4						
Inc≥1 CSBM/wk	28% (112/406)	**36%** (146/403)	**42%** (176/420)	26% (113/431)	**42%** (185/436)	**45%** (197/439)
≥3 CSBM/wk	13% (53/409)	**19%** (79/409)	**23%** (96/423)	14% (60/433)	**23%** (102/440)	**24%** (104/441)
Respond all 3 months All pts						
Inc≥1 CSBM/wk	15% (60/411)	**20%** (83/409)	**24%** (102/423)	15% (64/434)	**24%** (107/441)	**26%** (113/442)
≥3 CSBM/wk	8% (31/411)	10% (39/409)	**12%** (52/423)	7% (31/434)	**14%** (61/441)	**12%** (61/441)

About 43% of the Zelnorm 6 mg patients have an average increase of 1 or more CSBM during the first month compared to about 27% of the placebo patients; about half of these patients in each group are responders for all 3 months of the study. Only about 10% more of the Zelnorm 6 mg patients than placebo patients respond with a mean increase of 1 or more CSBM for all 3 months. The percentage difference is only 5% when looking at an average of 3 or more CSBM per week. So looking at the responder data by month shows statistically significant effects for Zelnorm 6 mg over placebo but also shows that less than 1/5 of the patients reap a benefit above placebo.

For the monthly data, averages are computed based on four weeks of data so being a responder does not imply that a patient responds at each of the 4 weeks. To determine how patients fared overall, this reviewer looked at the data in two ways; 1) the average daily change in CSBM for the full 12 weeks (Table 3.10) and 2) the number of weeks responding (Table 3.12). Both analytical approaches showed significant treatment effects for the 6 mg dose.

The selection of patients for this study is an important issue for the medical review team so the results of subgroup analyses aid in the interpretation of the efficacy of Zelnorm and its use. Analyses of the following subgroups revealed treatment effects (Zelnorm-placebo) consistent with the overall effects:

- baseline laxative users and non-users
- non-users of laxatives during the entire trial
- non-IBS-like patients (applicant's analysis)
- by baseline CSBM and baseline SBM
- by years of constipation
- by main constipation complaint except those patients complaining of abdominal pain

Notable inconsistencies in subgroups are the following:

- The interaction of treatment by gender was borderline significant at p=0.11. Males showed a smaller nonsignificant treatment effect (about 6-9% on both responder variables) compared to a treatment effect of about 10-17% for females (Table 4.2)

with the largest difference seen for the primary efficacy variable.

- The interaction of treatment by age was significant at p=0.04. The treatment effect for older patients was generally less than half the effect seen for younger patients.
- Patients with a main constipation complaint of abdominal pain (about 12% of the patients) had a treatment effect for the 6 mg dose about one-third the effect seen for the overall population (Table 4.5).

Overall comments:

- A dose response was seen in Study 2301 but not in Study 2302 for reasons for discontinuation (Tables 3.2 and 3.3) and for efficacy (tables 3.9 and 3.10 and Figure 3.1).
- Analyses of both change in CSBM and total number of CSBM consistently showed, regardless of statistical method or variable definition (e.g. by month, by week, observed, etc.), statistically significant treatment effects for Zelnorm 6 mg BID over placebo.
- The mean treatment effect for the 6 mg dose over placebo is an increase of less than 1 CSBM/week. About 42% of the Zelnorm 6 mg patients and 26% of placebo patients had an increase of 1 or more CSBM/week during the first month of treatment.
- About 40% of Zelnorm patients did not experience 3 or more CSBM at any week on trial. Zelnorm 6 mg patients who completed the trial had 3 or more CSBM for a median of 2 to 3 weeks out of 12 weeks (Table 3.12) compared to about 1 week for placebo.
- Laxative used was high at baseline (about 53%) with most patients continuing to take laxatives on study (Table 3.6). There was a small decline in laxative use in the 6 mg dose group with the odds of using laxatives decreasing significantly compared to placebo (p<.03). Also the number of weeks of laxative use was statistically significantly less for the 6 mg group than for the placebo group though the numerical mean difference was very small (<1 week). The distributions for the groups are shown in Appendix 7. So a decline in laxative use is seen but may be clinically insignificant.
- Since inconsistent results are seen for males and most of the patients studied were females, it seems that the results for females cannot be readily generalized to males.
- Only 13% of the patients were 65 or older; older patients showed a significantly smaller treatment effect than younger patients. So Zelnorm has shown minimal efficacy in a subgroup that may comprise a large part of the target population.
- Withdrawal of Zelnorm in Study 2302 resulted in a significant drop in CSBM's and responders (Figure 3.2).
- Only about 37% of the patients randomized to Zelnorm in Study 2301 were able to complete the 13-month extension study. Efficacy data was not adequate to determine maintenance of the Zelnorm effect.

5.3 Recommendations

No recommendations are being made in this draft review at this time regarding approval or labeling because this indication for Zelnorm will be discussed at an advisory committee on July 14, 2004.

Appendix 1. Details regarding diary assessments as described in the protocols

Extracted from the applicant's study reports

Daily diary assessments

Diary assessments will begin at baseline and continue through the withdrawal period.

Patients will be asked to record the following information in the diary on a daily basis:

- Time of intake of study medication for the first day of treatment.
- When a bowel movement is experienced, they will be asked to record, for each bowel movement:
  1. Time of bowel movement.
  2. Feeling of complete evacuation after the bowel movement (yes/no).
  3. Straining (no straining, acceptable staining, too much straining).
  4. Stool form

  Stool form will be assessed using the Bristol Stool Form Scale[13], which describes the stool according to 7 types (Appendix 3 below).
- Time of intake of bisacodyl tablets, number of bisacodyl tablets taken.
- Name and time of intake of any other concomitant medication.

Weekly assessments

In addition, patients will be asked to complete weekly diary assessments on the satisfaction with bowel habit, and on constipation symptoms, abdominal distension/bloating, and abdominal discomfort/pain.

Table 3-3 Weekly diary assessments

Question asked to the patient	Scale
How satisfied were you with your **bowel habits** over the past week?	0. a very great deal satisfied 1. a good deal satisfied 2. moderately satisfied 3. hardly satisfied 4. not at all satisfied
How bothersome was your **constipation** over the past week?	0. not at all 1. hardly 2. moderately 3. a good deal 4. a very great deal
How bothersome was your **abdominal distension/bloating** over the past week?	0. not at all 1. hardly 2. moderately 3. a good deal 4. a very great deal
How bothersome was your **abdominal discomfort/pain** over the past week?	0. not at all 1. hardly 2. moderately 3. a good deal 4. a very great deal

Appendix 1. Details regarding diary assessments (continued)

Applicant's Appendix 3 in Protocol for Study 3201

Appendix 3: Patient Diary

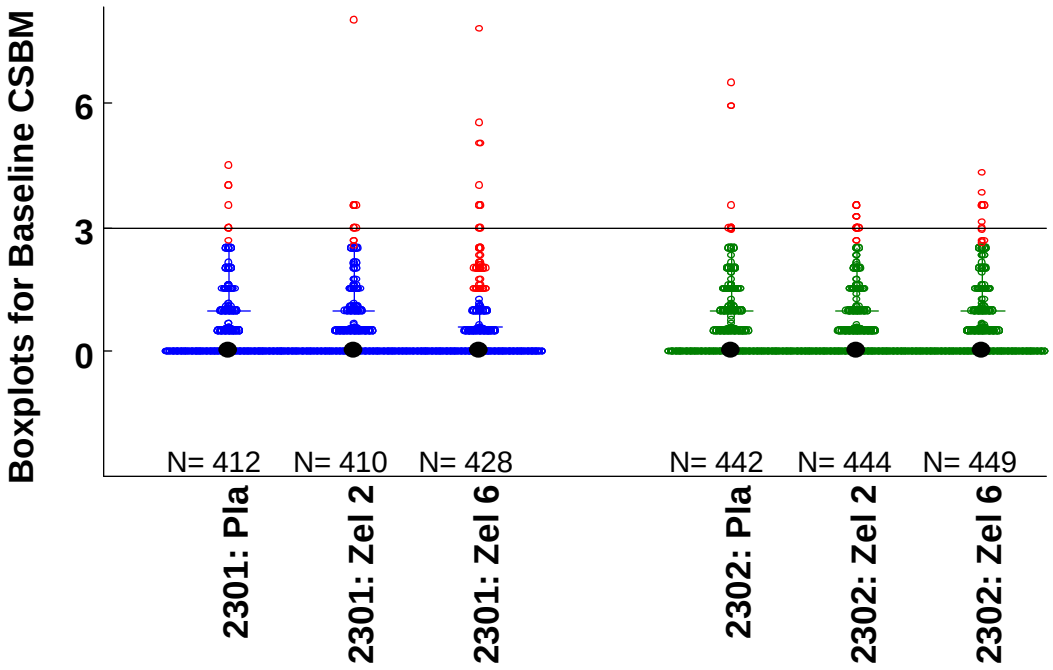
The Bristol Stool Form Scale[11]

Stool form	Appearance	Type
Separate hard lumps, like nuts (hard to pass). Result of slow transit		1
Sausage-shaped but lumpy		2
Like a sausage but with cracks on its surface		3
Like a sausage or snake-smooth and soft		4
Soft blobs with clear cut edges (easy to pass)		5
Fluffy pieces with ragged edges, a mushy stool		6
Watery, no solid pieces. Result of very fast transit		7

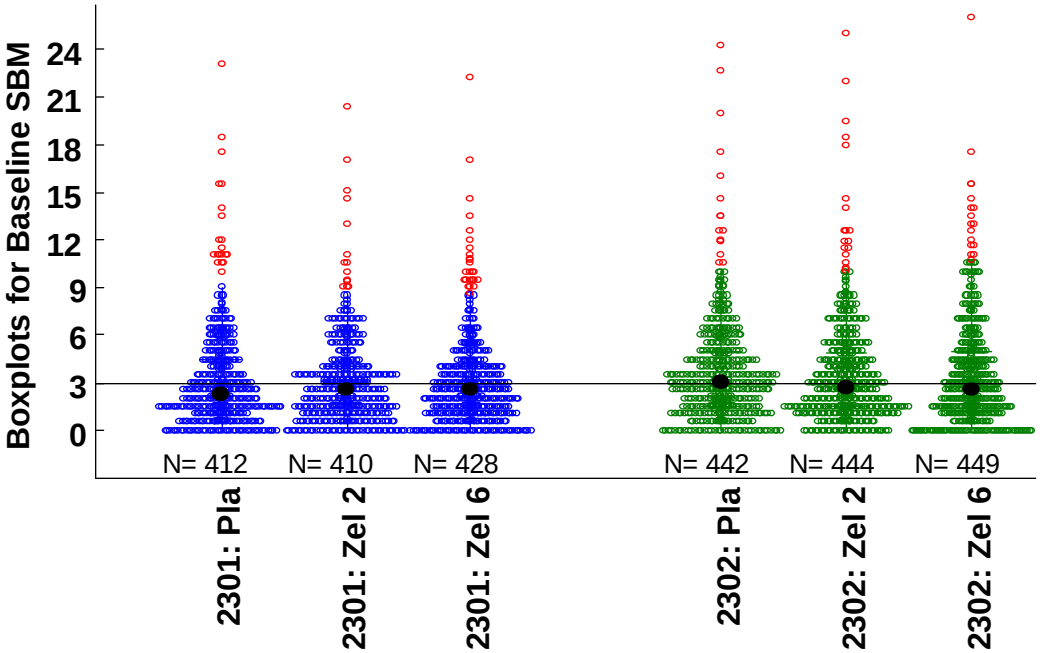
Appendix 2. Baseline CSBM and SBM by treatment and study

Baseline is reported as BM's per week and is computed from 2 weeks of baseline data

Baseline CSBM

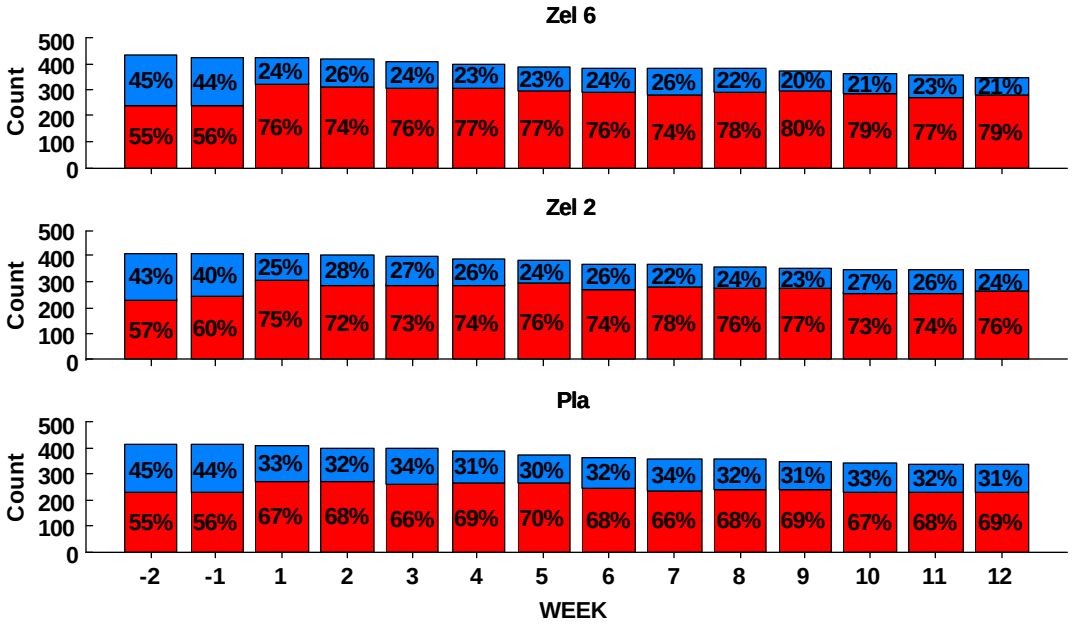


Baseline SBM



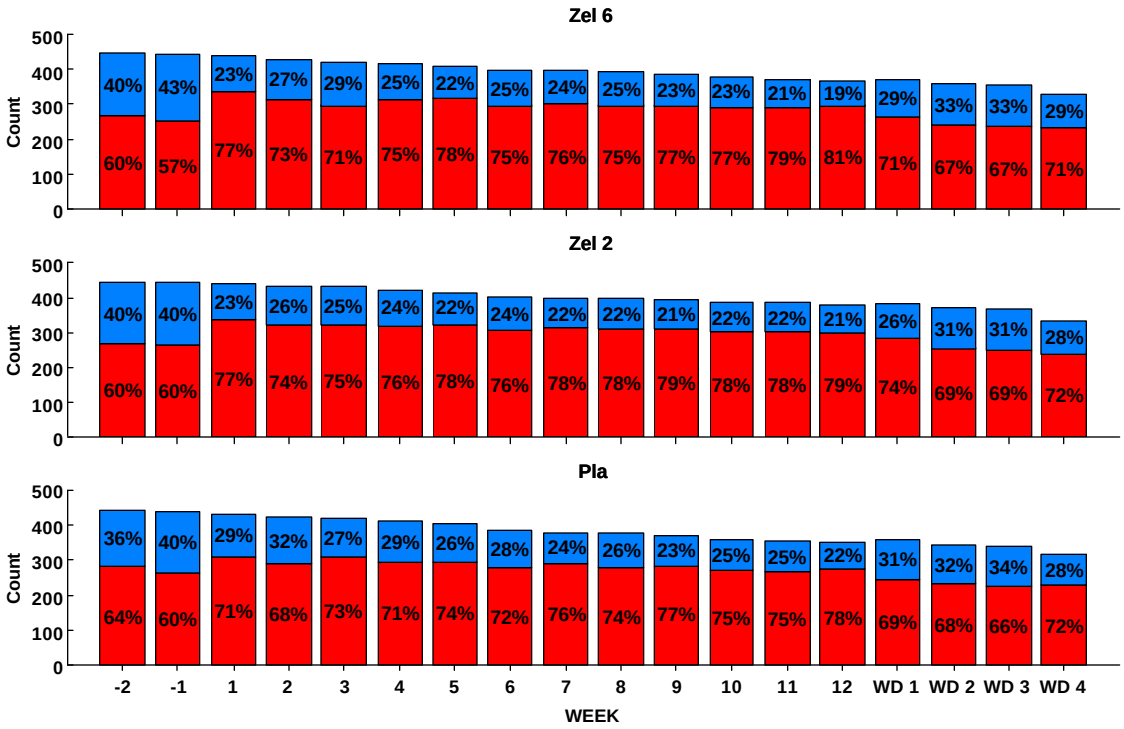
Appendix 3. Percent of patients using any laxatives by week on study

Study 2301



Blue indicates the % of patients taking at least one laxative during the week.

Study 2302



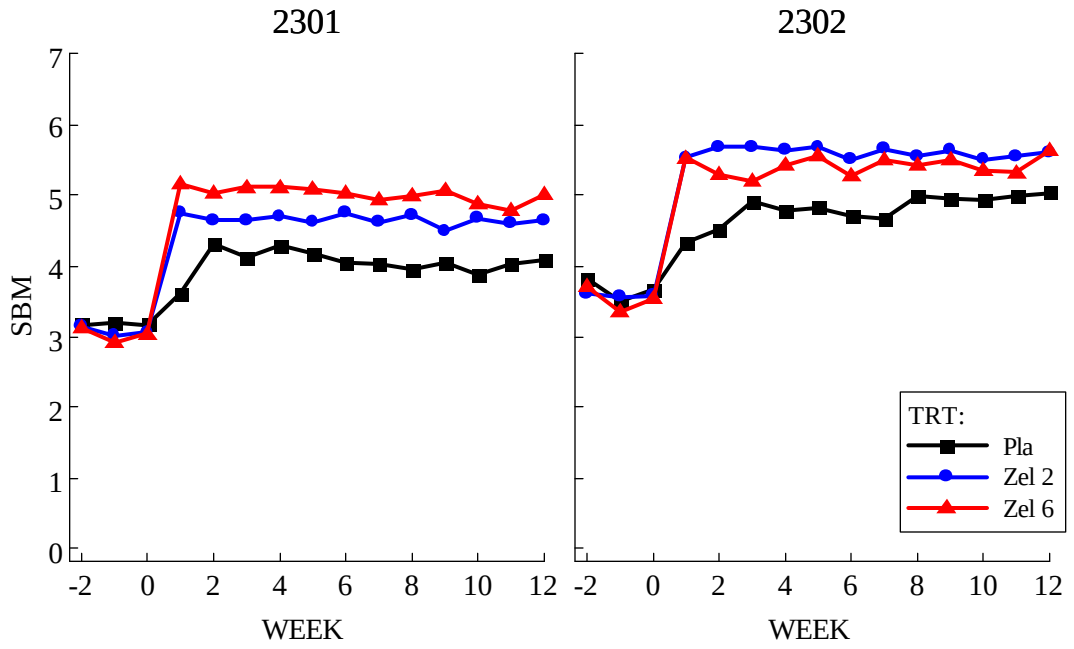
Appendix 4. Applicant's table of results for secondary endpoints

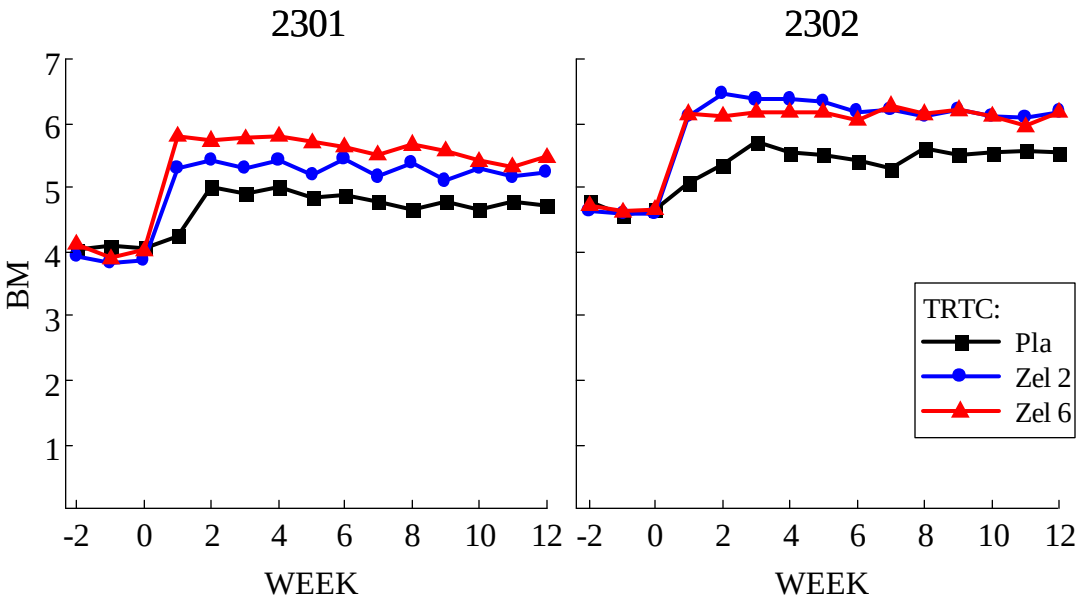
Table 4-3 Changes from baseline to Weeks 1-12 of individual constipation symptoms (ITT patients, studies E2301, E2302)

	Study E2301			Study E2302		
	Tegaserod 2 mg b.i.d. N = 417	Tegaserod 6 mg b.i.d. N = 431	Placebo N = 416	Tegaserod 2 mg b.i.d. N = 450	Tegaserod 6 mg b.i.d. N = 451	Placebo N = 447
Daily diary data (mean changes from baseline)						
Average number of CSBM/week	1.0	**1.3***	0.8	**1.4***	**1.3***	0.7
Average number of SBM/week	**1.6***	**2.0***	0.9	**2.0***	**1.9***	1.0
Average number of BM/week	**1.4***	**1.7***	0.8	**1.6***	**1.5***	0.7
Stool form score† for SBM	**0.7***	**1.0***	0.4	**0.6***	**0.8***	0.4
Daily straining score†† for SBM	- 0.3	**- 0.3***	- 0.2	**- 0.3***	**- 0.4***	- 0.2
Percentage of SBM with sensation of complete evacuation	12.5	18.4	14.3	**17.0***	**17.6***	10.4
Weekly questions from diary††† (mean changes from baseline)						
Global constipation relief score	**- 0.6***	**- 0.6***	- 0.4	**- 0.6***	**- 0.6***	- 0.4
Bothersomeness of constipation	**- 0.6***	**- 0.7***	- 0.5	**- 0.6***	**- 0.7***	- 0.4
Bothersomeness of abdominal distension/bloating	**- 0.5***	**- 0.5***	- 0.4	**- 0.7***	**- 0.6***	- 0.4
Bothersomeness of abdominal discomfort/pain	**- 0.4***	**- 0.4***	- 0.3	**- 0.5***	**- 0.4***	- 0.2
Satisfaction with bowel habits	**- 0.7***	**- 0.7***	- 0.5	**- 0.8***	**- 0.8***	- 0.5

CSBM = complete spontaneous bowel movement, SBM = spontaneous bowel movement
* Statistically significant versus placebo ($p<0.05$)
† Evaluated using a 7-point scale (1 to 7), where low values indicate harder stools
†† Evaluated using a 3-point scale (0 to 2): no straining, acceptable straining, too much straining
††† Evaluated using a 5-point ordinal scale (0 to 4) with low scores indicating improvement in symptoms
Source: [Summary of Clinical Efficacy – Tables 3-16, 3-17]

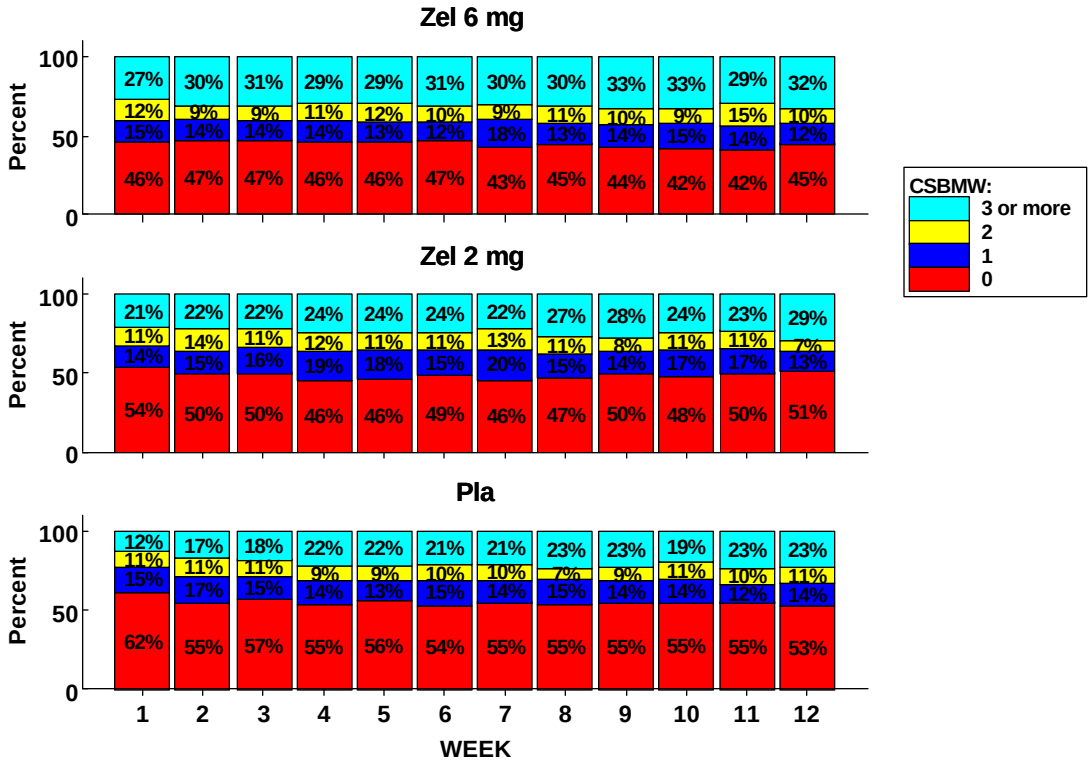
Appendix 5. Plots of Mean SBM and Mean Total BM



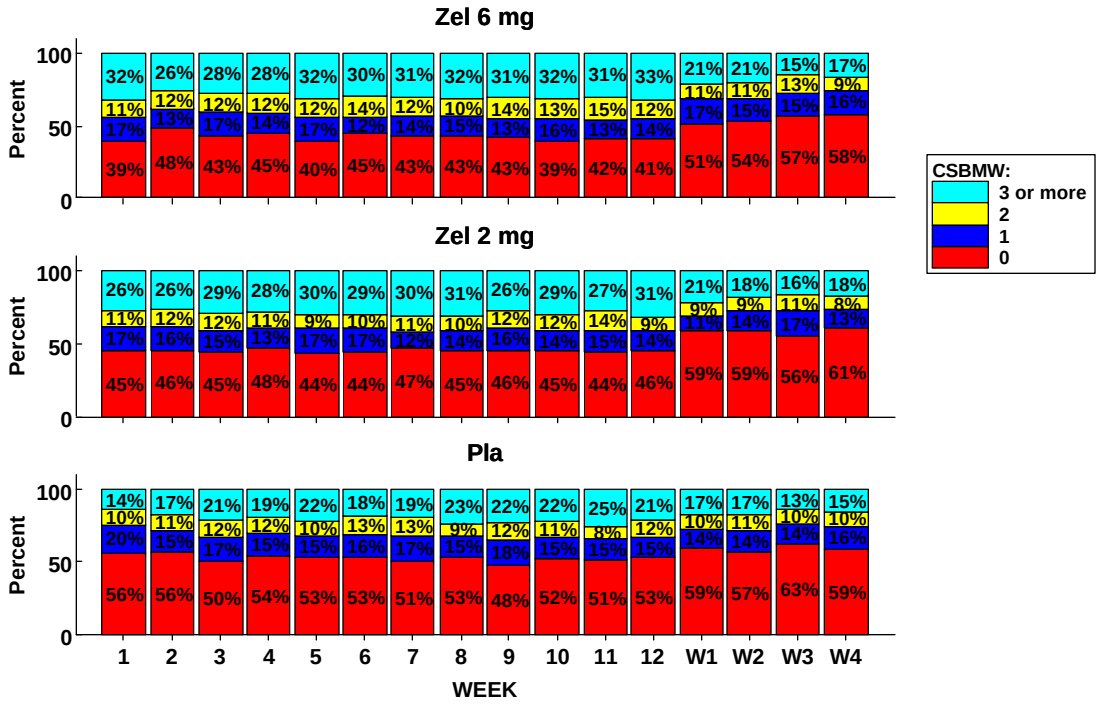


Appendix 6. Percent of patients by number of weekly CSBM

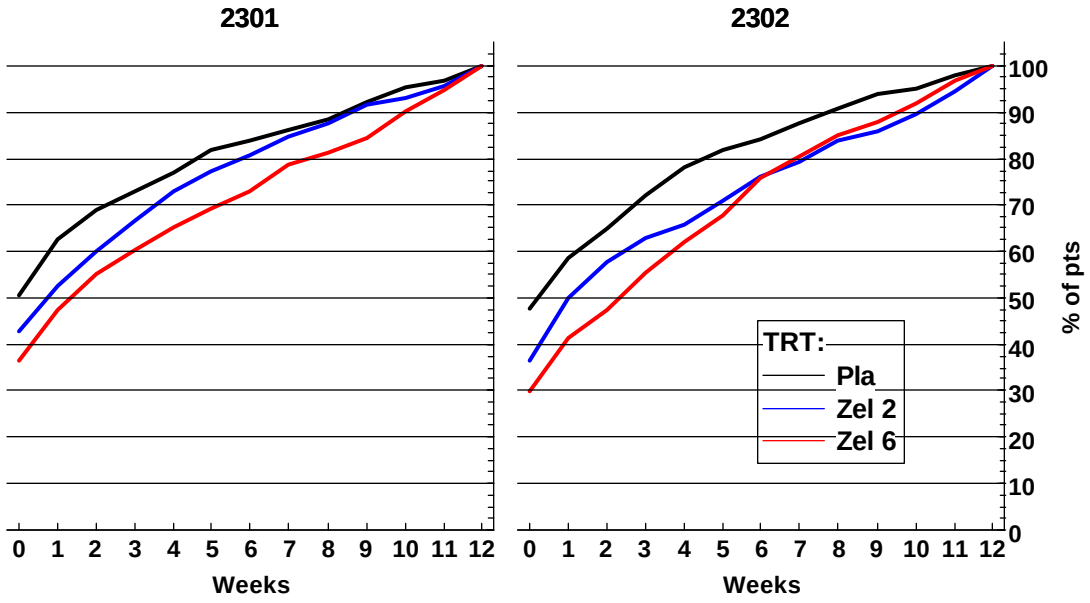
Study 2301



Appendix 6. Percent of patients by number of weekly CSBM (cont.)
Study 2302



Appendix 7. Cumulative distribution plot of number of weeks with 3 or more CSBM by study for patients who completed the full 12 weeks on study



The following is an example of how to interpret this graph: Looking at the graph on the right and the 60% line, 60% of the placebo patients had 3 or more CSBM per week for 1 or 0 weeks. Note that the lower the line, the more patients responding, more weeks.

If viewing this in black and white, the upper line in both graphs is placebo and the lowest line, Zelnorm 6 mg.

Appendix 8. Applicant's Subgroup Results for IBS-like and non-IBS-like Patients

Table 3-3 Responders (increase ≥ 1 CSBM/week from baseline) in weeks 1-4 by feature sub-group (pooled analysis, ITT population)

Sub-populations	Tegaserod 2 mg bid N=867	Tegaserod 6 mg bid N=882	Placebo N=863
Patients with IBS-type features			
n	203	202	188
Number of responders (%)	70 (34.5)	69 (34.2)	48 (25.5)
Odds ratio[1]	1.79	1.71	
95% CI for odds ratio	1.09, 2.92	1.04, 2.81	
p-value	0.0209	0.0332	
Remaining ITT patients			
n	651	675	666
Number of responders (%)	260 (39.9)	297 (44.0)	173 (26.0)
Odds ratio[1]	2.01	2.51	
95% CI for odds ratio	1.57, 2.59	1.96, 3.21	
p-value	<0.0001	<0.0001	

[1] An odds ratio >1 favors tegaserod over placebo

Table 3-6 Responders (≥ 3 CSBM/week) in weeks 1-12 by feature sub-group (pooled analysis, ITT population)

Sub-populations	Tegaserod 2 mg bid N=867	Tegaserod 6 mg bid N=882	Placebo N=863
Patients with IBS-type features			
n	203	202	188
Number of responders (%)	34 (16.7)	39 (19.3)	27 (14.4)
Odds ratio[1]	1.50	1.54	
95% CI for odds ratio	0.78, 2.89	0.80, 2.97	
p-value	0.2209	0.1948	
Remaining ITT patients			
n	651	675	666
Number of responders (%)	137 (21.0)	168 (24.9)	90 (13.5)
Odds ratio[1]	1.97	2.69	
95% CI for odds ratio	1.41, 2.75	1.94, 3.72	
p-value	<0.0001	<0.0001	

[1] An odds ratio >1 favors tegaserod over placebo

Appendix 9. Boxplots of baseline CSBM and baseline SBM by main complaint at screening